

NASA Conference Publication 005

# The Use of Nonhuman Primates in Space

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Proceedings of a symposium held at  
Ames Research Center  
Moffett Field, California  
December 2-4, 1974

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# The Use of Nonhuman Primates in Space

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## INTRODUCTION

Richard C. Simmonds

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Since man first started probing the frontiers of space, he has sent animals ahead to determine the safety of the new environment. The earliest animal astronauts were a duck, a rooster, and a sheep, which were flown into near-space in the basket of a balloon in the late 18th century. However, as the space vehicles became more complicated and our reach extended to Earth orbital flights, and beyond to the moon, the use of animals more physiologically similar to man was begun. In the race to develop manned space vehicles, the United States opted to use nonhuman primates as test subjects to prove the safety of the flight systems. During these early flights, the main parameter under study with the animals was simple survival, but as the space programs matured, the scientists began to study in detail the physiological and pathological effects of the space environment on the various biological systems.

As in the early days of space exploration, the first biomedical studies used simple organisms, and it was not until 1957 when the Soviet Union launched Sputnik II with the dog "Layka" on board that a higher vertebrate was used for a true biomedical study in orbital space flight. The United States continued to use nonhuman primates to "flight test" the various manned vehicle systems, and some physiological data were obtained from these flights, but only of a general nature (e.g., heart rate). It was not until 1969 that the United States flew a higher vertebrate on a dedicated biomedical mission (i.e., Biosatellite III with the pig-tailed macaque "Bonnie"). No biomedical studies using higher vertebrates were flown on any of the manned flights from the first Mercury flight through Skylab.

It is anticipated that the development of the reusable Shuttle Space Transportation System and its associated manned laboratory (Spacelab) will permit the accomplishment of critical and sophisticated experiments using a broad range of animal species. Without doubt, nonhuman primates will be included as subjects in Spacelab studies.

The objectives of this symposium were to provide a forum for the review of space-related biomedical research involving nonhuman primates and to provide expert advice to NASA engineers on the requirements for animal support hardware for future space-flight vehicles. The latter objective was achieved through the minutes of the meeting which detailed the various discussions held and which were distributed shortly after the symposium. The review of the status of nonhuman primate experimentation was accomplished by the presentation of papers by scientists eminent in this field. These proceedings are a compilation of most of those presentations.

# A REVIEW OF ANIMAL FLIGHT EXPERIMENTS

Harold Sandler

Ames Research Center

## SUMMARY

Animals have played a significant role in serving as precursors to man in space. This has been the case from the first balloon flights to the present. They have always preceded man in actual flight, particularly in those cases carrying a high risk. This has been true in the Soviet program as well as in the American space program. The American programs have utilized primates as the animal of choice; the Russians have used dogs. In each instance, monitoring of key physiologic parameters has been made and compared to the magnitude of environmental stresses. It is anticipated that these studies will continue as man's endurance is extended from the 89-day record presently held by Skylab to 6 months or year-long periods which will be required for accomplishing meaningful habitation in near-Earth orbit or travel to nearby planets.

## INTRODUCTION

The Space Age began over 17 years ago with the launching by the Russians of Sputnik I, the first vehicle to orbit the Earth, on October 4, 1957. Explorer I was launched by the United States 4 months later on February 1, 1958. Many manned and unmanned satellites and test vehicles have been launched since that time (ref. 1). The first manned flights were made by the Soviet Union. Gagarin was placed in orbit in Vostok I on April 12, 1961 and returned safely the same day. Titov followed in Vostok 2 on August 6, 1961. Glenn accomplished the first American orbital flight in Mercury's Friendship 7 on February 20, 1962. Sixty orbital flights using human or animal subjects have been accomplished since the Space Age began. The United States has conducted 28 manned, 1 chimpanzee, and 1 monkey flights; the U.S.S.R. has had 21 manned, 6 dog, and 3 mouse flights. Before man ever ventured into space, much had been accomplished by many scientists of varied backgrounds to pave his way. It is the purpose of this review to trace that history, particularly as it has involved the use of subhuman primates, and detail the use of animal experimentation as it has supported and/or supplemented the manned space program.

Initial American efforts, as related to the use of biologic payloads, can be traced to the close of 1946, when a pioneering balloon flight was conducted at Alamogordo, New Mexico, December 17th, through the auspices of the National Institutes of Health, to study cosmic radiation in the upper Earth's atmosphere (ref. 2). Fungus spores were used. This first flight was a failure since the spore containers were not recovered. A year later, the flight was repeated using fruit flies. This time the biologic payload was retrieved after attaining an altitude of 106 miles above the Earth — no effects from cosmic radiation could be found. By 1950, the balloon program began to gain momentum and has continued until this day. During the years 1950 to 1954, over 30 separate flights were conducted. Mice, hamsters, fruit flies, cats, dogs, and finally, Rhesus monkeys were utilized, traversing to altitudes of 27,000 to 30,000 m (90,000 to 100,000 ft) and for durations of up to 28 hr.

Most recent flights have focused on studies concerning the effects of cosmic radiation upon central nervous system tissues. Findings to date have failed to demonstrate significant radiation effects at the limits of the Earth's atmosphere.

With the cessation of World War II and the capture of German V-2 rockets, both Russian and American scientists became acutely aware of and interested in suborbital test flights using such vehicles. During the 10-year period, 1947–1957, both groups utilized heavily instrumented rockets of German or their own design for the study of the ionosphere – on many flights biologic payloads were included to obtain information which subsequently allowed for the inclusion of man in an orbiting vehicle complex (refs. 3-6).<sup>1</sup>

## AMERICAN FLIGHTS

Early American efforts were conducted by a team of Air Force investigators, headed by Dr. James P. Henry, starting in June 1948 and continuing until May 1952. A series of eight vertical rocket flights was accomplished to obtain physiological information concerning the effects of suborbital space flight (ref. 7). A total of 7 anesthetized Rhesus, Cebus, or *Cynomolgus* monkeys was used as well as 14 unanesthetized mice. The monkeys were used to obtain physiological observations concerning changes of pulse and respiration rates, and arterial and central venous pressures during flight. Performance measurements were obtained by direct photography of the mice. The initial five flights were made in a V-2 rocket. The first was accomplished June 18, 1948, using a 4.0-kg Rhesus monkey named "Albert." The monkey was housed in a capsule, 0.9 m (3 ft) long and 37.5 cm (15 in.) in diameter, located in the nose cone of the rocket. The capsule was to be recovered by parachute upon ejection during descent. The first animal died on the launch pad due to failure of the life support system. The capsule was launched but was not recovered because of failure of parachute deployment, a problem which occurred in all five V-2 flights. Despite the failures, important accomplishments were made with this first flight: (1) a capsule capable of carrying a small nonhuman primate was constructed; (2) a system for telemetry of physiologic data was provided; and finally, (3) a biologic payload was successfully launched. Significant system problems, which still needed to be remedied, were an inadequate life support system and failure of capsule recovery. The life support system was corrected on the next flight, June 14, 1949. "Albert 2," another anesthetized Rhesus monkey, was launched to an altitude of 134 km (83 mi). Respiration rate and electrocardiograms were recorded up to the time of capsule impact. Onboard recording equipment demonstrated that the animal was lost on impact due to parachute failure. The primates in this series were secured in an extended and immobilized posture by nylon netting to a specially designed couch padded with sponge rubber. Electrocardiograms were recorded from subcutaneous needle electrodes placed in a leg and in the chest. Respiration was recorded by a thermocouple placed in a special rubber face mask. Peak launch acceleration was 5.5 G, reentry acceleration was 12–13 G. Sedation was accomplished by intravenous and/or subcutaneous morphine (2 mg/kg). Physiologic variables were amplified and transmitted by FM-FM modulations to ground stations at Holloman Air Force Base and the White Sands Proving Grounds rocket range. The third and fourth V-2 flights each carried a sedated *Cynomolgus* monkey who was similarly instrumented,

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<sup>1</sup> Also in *Fundamental Results and the Prospects for Soviet Biological Experiments in Outer Space*. Translation of manuscript by Ye. A. Il'in, Moscow, Academy of Sciences of the U.S.S.R., 1973.

but neither animal was recovered. In the last V-2 flight in the summer of 1950, a package containing an unanesthetized mouse and a motion picture camera was substituted for the monkey capsule. The behavior of the mouse was photographed for 1-sec periods at 4-sec intervals throughout the flight. The mouse died on impact, but the camera and film were recovered and analyzed to show that tactile and visual senses allowed for orientation during the brief period of weightlessness.

By December 1949, the United States had developed its own high-altitude, free-flight sounding rocket (Aerobee), as shown in figure 1. It was smaller in size than the V-2 rocket and was fix-finned stabilized. Nine months after the last V-2 mouse flight, on April 18, 1951, an Aerobee carried its first biologic payload, an anesthetized Cebus monkey, to altitude. ECG and respiration were measured as in the V-2 flights. Again, the animal was not recovered due to parachute failure. Five months later, on September 20, 1951, Aerobee 2 accomplished the first totally successful rocket flight. An instrumented, anesthetized Rhesus monkey and 11 unanesthetized mice were taken to an altitude of 70,800 m (236,000 ft) and parachuted safely to the ground. In addition to ECG and respiration, arterial and central venous pressures were measured from small polyethylene catheters connected to appropriate statham pressure transducers. To prevent clotting, the catheters were continuously flushed by two automatic syringes at 4 ml/hr, using heparinized saline. Nine mice were placed in a separate compartment to study the effects of cosmic radiation. Two mice were placed in a special drum, 15 cm (6 in.) in diameter, rotating about an axis transverse to the long axis of the rocket at 12 rpm. The drum was divided into two halves; a normal animal was placed in one half, an animal labyrinthectomized by electrocautery of the horizontal semicircular canals was placed in the other half. Each compartment contained a small paddle over which the mice had to climb. Performance of both animals was recorded on motion picture film. The labyrinthine-defective animal did not become disoriented or exhibit abnormal behavior while weightless. The normal animal, in contrast, exhibited marked difficulty in orientation. Although parachute deployment was successful in this flight, there was a significant delay in reaching the capsule, which was exposed to the hot environment of the desert. The apparently uninjured monkey died enroute to the base from heat exposure, the mice survived. Aerobee 3, the last flight of the series, was launched nearly 1 year later on May 21, 1952. Two Cebus monkeys ("Mike" and "Patricia") were used, one placed in a seated position to receive  $+G_z$  ("Mike") and the other in a supine position to receive  $+G_x$  ("Patricia"). ECG's were obtained from both animals. Attempts to measure arterial and venous pressures failed. The performances of two mice were again photographed, one normal, the other labyrinthectomized. Movies of the drum, this time rotating at 4 rpm, again showed that the labyrinthine-defective mouse did well, if given a foothold, while the normal animal did not. Both monkeys and mice survived the flight without demonstrable ill effects. "Patricia" died 2 years following the flight from an infection secondary to an arm bite incurred while fighting. "Mike" continues to live and has had normal offspring subsequent to mating in 1960. A summary of physiological data from the rocket flights is shown in table 1 and figure 2. Figure 3 illustrates the respiration and ECG data from one of the animals flown in V-2 flight.

By 1958, rocket design had developed to the point where suborbital flights were possible. A mouse ("Wickie") was sent 2255 km (1400 mi) into space in April 1958 by van der Wal in the nose cone of an Air Force Thor-Able missile combination in the Mouse in Able (MIA) program (ref. 8). The project was designed to study the physiological response of mice to a 20-min period of weightlessness. The experiment was not recovered nor were the following two flights ("Laska" and "Benji"). The mice did survive reentry into the atmosphere, and physiological data were telemetered; the biologic capsules were not recovered.

On December 13, 1959, Graybiel and his team launched Bioflight 1, the first unanesthetized monkey known to have traveled in the nose cone of a ballistic missile (ref. 9). A Jupiter rocket carried a 0.5-kg squirrel monkey (*Saimiri sciurea*), named "Old Reliable," to a 483-km (300-mi) altitude over a down-range distance of 2093 km (1300 mi). A typical Jupiter trajectory is shown in figure 4. Telemetered data were received by ground stations for 13.3 min; the animal was not recovered. The capsule for housing the animal was 25.4 cm (10 in.) in length, 34.9 cm (13-3/4 in.) wide, and averaged 12.7 cm (5 in.) in depth, (approximately 12,348 cm<sup>3</sup> (790 in.<sup>3</sup>)). When finally instrumented, including the monkey, the capsule weighed 13.3 kg. Measurements were made of heart rate (subcutaneously implanted wire mesh platinum electrodes), respiration rate (glass bead thermistor), heart sounds (variable-reluctance magnetic pickup placed on anterior chest wall), body temperature (glass probe thermistor in left axilla), cabin temperature, pressure, and radiation (nuclear track plate). The life support system functioned satisfactorily, as did all biosensors except for respiration, which was lost early in flight. Less than 6 months later on May 28, 1959, the same group of investigators launched Bioflight 2, using two monkeys, "Abel" — a 3.2-kg Rhesus, and "Baker" — a 0.5-kg squirrel monkey. Both animals were successfully recovered. All variables measured during Bioflight 1 were again measured here; colonic temperature replaced axillary measurements and electromyograms (EMG's) were added. The total weight of the capsule system, including the animals, was approximately 116.1 kg and required significant ingenuity in inserting the animal packages since the Jupiter nose cone had not been designed to accommodate this larger biologic payload. "Abel" was placed in the nose cone 3 days prior to flight, while "Baker" (the smaller capsule) was loaded 6 hr prior to takeoff. During the 64-hour countdown period, "Abel" was fed by intraperitoneal infusion of 5 percent dextrose in water at the rate of 5 cm<sup>3</sup>/hr. Body wastes (urine and feces) were allowed to accumulate in diapers. An attempt was also made to obtain the first in-flight performance data when "Abel" was trained to tap a telegraph key-like switch each time a red light flashed in the capsule; data transmission from the performance tester ceased just before takeoff. "Abel" died 5 days postflight from anesthesia associated with removal of the subcutaneously implanted ECG electrode. "Baker" came through the flight completely unharmed and is still alive. Measurements made on all three animals during various phases of the flights failed to show significant changes from prebaseline values or from ground-based controls.

Scarcely a week after the historic "Abel-Baker" flight, the United States sent four C57Bl mice aloft in a Discoverer 3 satellite from Vandenberg Air Force Base on June 3, 1959 (ref. 1). This was the first American attempt to orbit a biologic payload. The Discoverer failed to go into orbit, and the animals were lost.

The next American animal flight occurred on December 4, 1959, at Wallops Island, when Green and coworkers sent a 3.6-kg male Rhesus monkey ("Sam") to an altitude of 84,000 m (280,000 ft) on a Little Joe solid fuel launch vehicle. The flight was repeated to an altitude of 14,700 m (49,000 ft) on January 21, 1960, with a 2.7-kg female ("Miss Sam"). Both animals were successfully recovered. These flights were used to verify the adequacy of the flight equipment to be used in Project Mercury (manned space flight program), which was to follow. They were specifically used to evaluate the biomedical effects of the acceleration experienced during the abort of a Mercury flight after liftoff. Neither animal demonstrated findings of note. The biologic capsule used was a sealed cylinder 0.9 m (3 ft) long, 0.45 m (1-1/2 ft) in diameter, and carried a 18.2-kg (40-lb) oxygen supply. For the first time in any animal effort, a performance test was included and successfully recorded. The same performance tasks given "Abel" were used. "Miss Sam's" performance was not as good as "Sam's."

In October 1960, Clamann and others launched three C57Bl mice ("Sally," "Amy," and "Moe") to 650 miles altitude over a 5000-mile range (ref. 10). The flight was boosted by an Atlas RZX-2A missile, and the nose cone was successfully recovered. Although the capsule did not go into orbit, it provided important biologic information since it passed through the inner Van Allen radiation belt. The animals showed no effects from the radiation exposure individually or in their subsequent offspring.

A team, again headed by Dr. James Henry, in 1961 was the first to use chimpanzees to test missile-vehicle complexes prior to their use by man (ref. 11). "Ham," a 16.7-kg chimpanzee, on January 31, 1961, preceded Commander Allan Sheppard in ballistic space flight reaching a speed of 9340 kmph (5800 mph), an altitude of 251 km (156 mi), and extending over a range of 667 km (414 mi). A Mercury capsule was used, powered by a Red Stone booster (MR-2). Recorded physiologic data and flight characteristics are shown in figure 5. Recordings were made of lead I and lead III of the electrocardiogram, respiratory waveform, rectal temperature and two psycho-motor tests (discrete and continuous avoidance tasks). ECG electrodes consisted of stainless steel wires threaded subcutaneously. Wire mesh electrodes were also placed on the thighs in advanced testing for subsequent use in man. Respiration was recorded by a pneumograph, consisting of a rubber tube filled with saturated copper sulfate solution. Temperature was recorded by a rectal thermistor. "Ham" survived the flight without ill effects. The important findings were that an animal closely resembling man could survive the stress of suborbital flight and effectively perform a critical task throughout the flight period.

On November 29, 1961, "Enos" — an 18.9-kg male chimpanzee — preceded Astronaut John Glenn in orbital flight spending 183 min in weightlessness (perigee 99 mi, apogee 146 mi). The flight was accomplished in a Mercury capsule powered by an Atlas missile (MA-5). The fully instrumented animal in his flight couch is shown in figure 6. In addition to ECG, respiration, body temperature, and psycho-motor tests, the following procedures were added: (1) a Foley catheter was inserted to collect all urine during flight, (2) the animal was diapered for feces collection, (3) arterial and venous pressures were recorded from intravascular catheters, and (4) zero-G food and water dispensers were included and operated successfully. Physiological data from the MA-5 flight is shown in figure 7. The blood pressure recording system was similar to that previously used in the Aerobee flights. Intravascular pressures were obtained by percutaneous catheterization of the right anterior tibial artery and saphenous vein, using PE 50 polyethylene tubing connected to appropriate Statham transducers. Catheters were flushed at a rate of 2.5 ml/hr, using heparinized saline. Outputs from the pressure transducers were recorded by means of a specially developed onboard galvanometer oscillograph and not transmitted by telemetry. Blood pressure values, as shown in figure 7, were high and most likely due to the stress of the instrumentation and flight procedures. Peak systolic values were not obtained due to the limits set for galvanometer deflection. Extra systoles were occasionally recorded during flight and were most likely due to the presence of the venous catheter in the right ventricular chamber, corroborated by the fact that pulmonary artery pressure was recorded throughout the flight. Both chimpanzee flights were highly successful in demonstrating the validity of the capsule environmental control system for subsequent use with man, and showed that the vehicles could be successfully recovered, and that short-term weightlessness could be experienced without adverse physiological effects. "Enos" died on November 4, 1962, approximately 1 year after his historic flight due to *Shigella* dysentery at Holloman Air Force Base. He had been ill for 2 months. A summary of all U.S. biologic experiments in suborbit is given in table 2.



Following the 1962 demonstration of man's ability to participate as part of the space vehicle complex, the focus of the American program has been the support of man in space. Over this period various biologic systems have been used in attempts to obtain basic information concerning the effects of weightlessness, to determine the dangers from radiation hazards for short- or long-term voyages, and to understand the physiological changes observed in astronauts during or after flight. Large-animal flight experiments, particularly the use of primates for these ends, have seen only limited or sparse use, since man himself has been utilized instead. A summary is shown in table 2. During the period 1960-61, various biologic systems, such as human serum, rabbit antisera, plant seeds, viruses, bacteria, and tissue culture cells, were exposed to weightlessness and radiation aboard Discoverer satellites (Discoverer XVII, XVIII, XXXII). No significant findings were made. During 1965 and 1966, human blood samples were flown aboard Gemini III and XI, frog eggs on Gemini VIII and XII. Conflicting results were obtained concerning radiation effects on white blood cells, while the prefertilized frog eggs developed normally.

Early in 1966, a series of dedicated bioscience satellites were begun to further investigate the fundamental effects of the space flight environment (primarily weightlessness and radiation) using various biologic payloads. This culminated in 1969 in a flight experiment (Biosatellite III) using a single pig-tailed monkey. Biosatellite I, launched December 14, 1966, carried a multitude of plant and cellular systems. It failed to deorbit after it completed its prescribed 3-day orbital flight. Biosatellite II, launched September 7, 1967, completed only 45 hr of its programmed 72-hr space journey. The satellite carried fruit flies, beetles, plants, cellular systems, viruses, and bacteria. Some systems demonstrated radiation effects; the majority showed slight or insignificant changes due to weightlessness and/or radiation. Biosatellite III was launched on June 28, 1969 and carried a 5.5-kg male pig-tailed monkey (*Macaca nemestrina*) (ref. 12). Figure 8 illustrates a cross section of the flight capsule and its contents. The flight lasted only 8.8 days of a planned 30-day mission and was terminated due to deterioration of monitored physiological parameters during flight. The monkey died shortly after the capsule was recovered and weighed 4.4 kg at the time of his demise on July 7, 1969. The cause of the animal's death is still a subject of controversy. Postflight findings demonstrated marked dehydration in a heavily instrumented animal. It is likely that the latter situation in combination with the stress of flight caused the animal's demise. At the time, it was speculated that the changes were due to weightlessness alone. Subsequent Russian and American animal and human flights lasting from 3-12 weeks have cast serious doubt on such a hypothesis. The experiment, which consisted of four ground-based controls and a single flight candidate, monitored brain states, behavioral performance, cardiovascular status, fluid and electrolyte balance, metabolic state, and radiation. Sensors were placed for 33 channels of physiologic data. These included 10 for EEG (electrodes implanted in the brain), 2 for EOG (electro-oculogram), 2 for EMG leads, 6 for cerebral and rectal temperature probes, catheters in both femoral arteries and saphenous vein, and a catheter for urine collection. A complex performance task was also provided. A zero-G food and water dispenser was used, and it operated well. The vascular pressure monitoring system was similar to that used previously in the Aerobee rocket launchings and chimpanzee orbital flights, and the in-flight cardiovascular data are shown in figure 9. Fluid balance data, body weight changes, and brain temperatures during flight are shown in figure 10. All data were telemetered. All monitoring systems operated well, but the restrained primate deteriorated after the 4th day in orbit, ceasing to eat or drink, becoming hypothermic and hypotensive, and did not respond to remedial measures in the immediate postflight period. Two of the ground-based controls, who were similarly instrumented, died shortly after the flight termination, casting serious doubt on the ability to use such highly instrumented animals for long-term physiological observations.

Continued use of biologic systems has occurred since 1969, but has not used primates as subjects. The most notable was the Orbiting Frog Otolith experiment. It was conducted in November 1970 to study the effects of weightlessness on vestibular nerve function. An onboard centrifuge was included for the first time to produce provocative stimulation to the central nervous system, and it operated successfully. The findings demonstrated vestibular adaptation by the fifth day of flight. Additional animal system models have been utilized as detailed in table 3 and have continued to provide new information concerning the nature of biologic adaptation to weightlessness, and the possible hazards associated with synergistic interactions of weightlessness and high-energy particle radiations as encountered in flight. Tables 4 through 10 summarize all American and Russian space flight experiments using biologic systems. Flights are listed in the chronological order in which they were flown, covering the period 1946 through 1973. The presence and use of primates during this period are emphasized where and whenever utilized.

## RUSSIAN FLIGHTS

Although Soviet investigators have not utilized primates in their space flight experiments, no review of the history of life sciences efforts in space, as demonstrated in tables 4 through 10, would be complete without mentioning their notable accomplishments. U.S.S.R. investigators have been the pioneers in space flight efforts (refs. 3-5, 12, 13). They launched the first orbiting space vehicle, Sputnik I, on October 4, 1957 (refs. 4, 13). One month later, Sputnik II was launched with the world's first biologic payload to orbit the Earth (dog "Layka"), and finally on April 12, 1961, they launched the first orbital manned flight. Early Russian and American biologic space efforts were similar in design, but differed in that dogs were the experimental animal of choice for Russian efforts, in contrast to the American use of primates. During the period 1949 to 1960, the Russians conducted a systematic test program progressing from small-rocket experiments to progressively large boosters which could finally reach an altitude of 450 km. A total of 40 animal flights occurred during this period - all using dogs. Most animals made multiple flights, certain animals - such as "Otvazhnaya" - made five flights; some were killed on the first or second flight. No dog was reported lost because of ECS failure but due to other "reasons," reminiscent of our parachute failures under similar circumstances. The objectives of these studies were to determine the effects of acceleration forces on the animals, to develop a retrieval system, and to record physiological functions during flight. ECG's were recorded during all flights, using nickel-plated discs. Blood pressure was measured, using an oscillographic method, from a carotid artery which had been brought out onto a skin flap. Respiratory frequency and EMG's were occasionally monitored (muscle of extremities or eye muscles). Motion pictures were also occasionally taken. Russian scientists concentrated their efforts on factors that might prove harmful for long-term existence in a flight environment, which included: (1) zero barometric pressure; (2) ionizing radiations (from ultraviolet or cosmic sources); (3) accelerations; and (4) drastic changes in heat exchanges between body and cabin and space environment. Protective measures were developed which included hermetically sealed cabins and insulated space suits.

Between 1949 and 1952, Galkin and coworkers sent a total of 9 dogs (3 flown twice) in hermetically sealed cabins to an altitude of approximately 100 km at velocities of 4200 km/hr (ref. 3). Decelerations of the nose cone began 4-1/2 min after launch, and parachute deployment was activated 5-1/2 min after launch. From 1953 to 1956, Bugrov and coworkers launched a total of 12 dogs (2 each time in separate compartments, 6 flights) (ref. 2). Cabins were not sealed;

animals wore ventilated space suits instead. Flights reached altitudes of 110 km and nose cone separation occurred 3 min after launch. Four min after launch (altitude 75 to 90 km), the animal in the right compartment was ejected at speeds of 460 to 730 mi/sec, and after 3 sec of free fall, a parachute was automatically deployed imposing an acceleration of 7 G on the animal who eventually landed about 1 hr after launch. When the capsule reached an altitude of 39 to 46 km (about 5 min after launch), the animal in the left compartment was ejected at speeds of 1000 to 1150 mi/sec. The animal free-fell to an altitude of 4 km at which time parachute deployment occurred.

Galkin and coworkers continued their work in capsule recovery systems in 1957 by launching a series of five dogs in hermetically sealed cabins to altitudes of 200 to 212 km (ref. 3). Periods of weightlessness up to 6 min were attained. At 4 km, the brake chute was opened, imposing a stress of 8 G; at 2 km, the basic parachute system was deployed, imposing about 4 G on the animal. Results of these studies showed that the dogs reacted to the acceleration, noise, and vibration environments of launch and recovery by increasing blood pressure, pulse frequency, and respiration rate, but these stresses were well within physiological tolerance limits.

On November 3, 1957, as a result of the work of Chernov and Yakolev, Sputnik II was placed in orbit carrying a female dog, "Layka" (ref. 6). This was the first biologic payload to be placed in Earth orbit. It was not recovered. The capsule was hermetically sealed and conical in shape. The animal died on the 6th day from hypoxia. The capsule disintegrated on reentry on April 14, 1958.

Four additional ballistic flights followed the orbital flight of "Layka" to better define orbital recovery systems. Two dogs, "Belyanka" and "Pestraya," were launched in August 1958 in hermetically sealed cabins to an altitude of 450 km. The objective, which was accomplished, was to recover the capsule in a "preselected area." In July 1959, two dogs and a rabbit were launched to a 160-km altitude and successfully recovered. In the same month, two more dogs were launched to an altitude of 160 km, but no record of the outcome of this flight is available. The last ballistic flight of record was conducted in June 1960, when two dogs and a rabbit were lifted to an altitude of over 160 km again, but data from this project has not been made available.

On May 15, 1960, Sputnik IV — containing a single dog — was placed in orbit to test orbital recovery systems. Recovery failed. The first successful telemetry to ground of biological information was accomplished. Records were obtained of respiratory frequency, arterial blood pressure, ECG (electrodes implanted in chest muscles in vicinity of fourth and fifth intercostal muscles), cabin temperature, and motor activity (EMG electrodes in paws).

On August 20, 1960, Sputnik V was launched and recovered 24 hr later. This flight represented the first successful recovery of a biologic payload from space. The satellite weighed 4500 kg and contained two female dogs, "Belka" and "Strelka." The capsule also contained 21 black and 21 white mice, several rats, scores of insects (fruit flies), seeds, and cellular organisms. "Belka" was 2-1/2 years old and weighed 4.5 kg; "Strelka" was 1-1/2 years old and weighed 5.5 kg. Both dogs were white in order to provide maximal visibility to onboard television cameras. This was the first flight in which successful TV transmission of information occurred. ECG's and blood pressures were monitored as on previous flights. The animals were fed by an automatic device. The food was a jelly-like substance which contained meat, water, and vitamins. Mice and rats were fed dry food briquettes; water was obtained from a wick.

On December 1, 1960, the Russians launched Sputnik VI which again contained two dogs, "Pchelka" and "Mushka," insects, and plants. The satellite orbited for 2 days and telemetered biologic data on physiologic functions. Heart performance was measured by a seismocardiographic (vibration-sensing) transducer in "Pchelka" and from phonocardiograms in "Mushka." EMG's and ECG's as well as deep body temperature (thermistors implanted in withers, pelvis) were obtained in both dogs. Television transmission was again successfully accomplished. A malfunction developed in the recovery system, and the satellite burned up in the atmosphere on reentry.

After several launch and recovery failures during the ensuing 3 months, Sputnik IX was launched on March 9, 1961. It weighed 4700 kg and was successfully recovered the same day. The satellite contained the dog "Chernushka" and a variety of biologic specimens including guinea pigs, black mice, insects, frogs, and seeds. These latter biologic systems were used primarily to test the effects of cosmic radiations prior to exposure of man. "Chernushka" weighed 5.9 kg and was used to test automatic blood pressure systems later used in man. Both radio and television coverage was obtained. The last flight in the Sputnik series (Sputnik X) was accomplished March 25, 1961 and recovered the same day. The flight was identical to the March 9th flight and used the dog "Zvezdochka." The satellite weighed 4695 kg. The objectives were to conduct the final tests of launch and recovery systems to be subsequently used in man. Successful completion of the flight led to the launching of Y. A. Gagarin in orbit 3 weeks later on April 12, 1961.

The last Soviet flight of note for the purposes of these discussions was launched on February 22, 1966 and returned safely 22 days later (ref. 13).<sup>2</sup> The satellite vehicle, Kosmos 110, contained two dogs, "Veterok" and "Ugolek"; mice, fruit flies, seeds, and cellular systems were also included. The dogs were partially restrained in a pod which allowed for collection of wastes by air convection and were fed by gastrostomy. ECG's, phonocardiograms, and carotid arterial tracings were obtained on both animals to determine systolic time intervals, which were subsequently used to assess cardiovascular status during flight. Analysis indicated a decrease in cardiac output and stroke volume for both animals. Attempts to withdraw blood and measure intravascular arterial pressure failed. Successful transmission of television pictures and onboard motion pictures were obtained. Both dogs lost weight; "Veterok" lost 2.0 kg from an initial weight of 7.6 kg; "Ugolek" lost 2.4 kg from an initial weight of 8.3 kg. The exact reasons have remained obscure. It is felt that the feeding system during flight did not provide adequate nourishment. Postflight findings showed evidence of bone calcium loss and effects of dehydration and poor food intake. This flight represented the last Russian large-animal experiment.

The last table, table 11, summarizes the Soviet experience with biologic payloads in space. In contrast to tables 2 and 3, it demonstrates that primates have not been used aboard Russian flights and that extensive experience has been gained with other small- and large-size vertebrates.

## CONCLUDING REMARKS

In conclusion, it can be stated that primates have occupied a significant position in the history of space flights. They have been used extensively in early American space flight experiments.

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<sup>2</sup> See footnote 1, page 4.

Attempts to use heavily instrumented animals in more recent flights have demonstrated associated problems which require attention for correction in future attempts. Extensive experience with biologic systems has been obtained with a variety of vertebrate species over the past 18 years. These results demonstrate a need for further in-depth in-flight investigations and a continuing role for subhuman primate experiments.

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TABLE 1.- AEROBEE I AND II - PULSE AND RESPIRATION RATES

	PULSE RATE PER MINUTE				RESPIRATION PER MINUTE			
	CONTROL	POWERED ASCENT	SUBGRAVITY	FREE FALL	CONTROL	POWERED ASCENT	SUBGRAVITY	FREE FALL
APPROX. TIME IN SECONDS		0-50	50-200	200-400		0-50	50-200	200-400
ACCELERATION	1 g	4-6 g	0.1 g	1 g	1 g	4-6 g	0.1 g	1 g
EXPT. NO. V <sub>2</sub> <sup>a</sup>	190	110	190-180	-	90	60	65-60	-
V <sub>2</sub> <sup>b</sup>	190	200	210-200	200	40	50	60-50	
AEROBEE I	210	220	190-185	220	60	65	60-20	60
AEROBEE II	166	172	178-178	175				
MEAN	190	175	190-185	205	60	60	60-40	60

TABLE 2.- SUMMARY OF ALL U.S. BIOLOGIC EXPERIMENTS IN SUBORBIT

	BALLOON FLIGHTS 1946-1956	V-2 1948-1950	AEROBEE 1951-1952	THOR-ABLE MIA-1958	JUPITER 1958	DISCOVERER III 1959	LITTLE JOE 1959-1960	ATLAS RVX-2A	REDSTONE MERCURY 1961	ATLAS MERCURY 1961
VIRUSES & BACTERIA	●									
PLANT SEEDS	●									
INVERTEBRATES	●									
MICE	●	●	●	●		●		●		
CATS	●									
DOGS	●									
PRIMATES	●	●	●		●		●		●	●

TABLE 3.— U.S. BIOLOGIC EXPERIMENTS IN EARTH ORBIT

	DISCOVERER XVII	DISCOVERER XVIII	DISCOVERER XXXII	GEMINI III	GEMINI VIII	GEMINI IX A	AGENA VIII	GIMINI XI	GEMINI XII	OVI-4	BIOSATELLITE I (a)	BIOSATELLITE II	BIOSATELLITE III	OFO I	APOLLO 16	APOLLO 17
BIOCHEMICAL SYSTEMS	•	•							•							
VIRUSES & BACTERIA	•					•	•		•		•	•			•	•
CELLULAR SYSTEMS		•		•	•			•	•	•	•	•				
TISSUES		•													•	•
PLANT SEEDS			•								•	•			•	•
HIGHER PLANTS											•	•				
INVERTEBRATES											•	•			•	•
AMPHIBIANS														•		
PRIMATES													•			

(a) FAILED TO DE-ORBIT AFTER 72 HOURS-NATURAL ORBITAL DECAY WITH RE-ENTRY AFTER 60 DAYS-RECOVERY FAILED

TABLE 4.— SPACE BIOLOGY — EARLY STUDIES (1946–1960)

- 1946 — 1952 — BALLOONS AND BALLISTIC ROCKETS (SIMPLE EXPERIMENTS WITH FRUIT FLIES, MICE, RATS AND CATS)
- 1957 — SOVIET SPUTNIK 2 WITH THE DOG "LAYKA"
- 1958 — SQUIRREL MONKEY ("OLD RELIABLE") IN JUPITER BALLISTIC MISSILE
- 1958 — TWO MONKEYS IN JUPITER BALLISTIC MISSILE ("ABLE" (RHESUS) AND "BAKER" (SQUIRREL))
- 1959 — RHESUS MONKEY IN LITTLE JOE BALLISTIC MISSILE ("SAM")
- 1960 — SOVIET SPUTNIKS 4 & 5 WITH DOGS, SMALL LABORATORY ANIMALS, AND PLANTS
- 1960 — RHESUS MONKEY IN LITTLE JOE BALLISTIC MISSILE ("MISS SAM")
- 1960 — DISCOVERER 17 & 18 MISSIONS WITH TISSUE CULTURES (TC), BACTERIAL SPORES, ALGAE, & SERUM PROTEINS

TABLE 5.— SPACE BIOLOGY — EARLY STUDIES (1961)

- 1961 — SOVIET SPUTNIKS 6 & 7 WITH DOGS, SMALL LABORATORY ANIMALS, TC, INSECTS, PLANTS, ASCARID EGGS, & MICROORGANISMS
- 1961 — SOVIET VOSTOKS 1 & 2 WITH TC, INSECTS, PLANTS AND BACTERIA
- 1961 — JANUARY — MERCURY BALLISTIC FLIGHT WITH CHIMPANZEE ("HAM")
- (APRIL 1961 — YURI A. GAGARIN — FIRST SOVIET COSMONAUT — ORBITAL)
- (MAY 1961 — ALLEN B. SHEPPARD — FIRST U.S. ASTRONAUT — MERCURY 3 BALLISTIC FLIGHT)
- 1961 — NOVEMBER — MERCURY BALLISTIC FLIGHT WITH CHIMPANZEE ("ENOS")
- 1961 — NOVEMBER — BIOS I & II ORBITAL FLIGHT WITH NEUROSPORIA, E. COLI, HUMAN LEUKOCYTES, GRASSHOPPER NEUROBLASTS, BARLEY SEEDS, AMOEBA, AND SEA URCHIN EGGS

TABLE 6.— SPACE BIOLOGY — EARLY STUDIES (1962–1965)

1962 — SOVIET VOSTOKS 3 & 4 WITH INSECTS, PLANTS, & MICROORGANISMS  
1963 — SOVIET VOSKOKS 5 & 6 WITH INSECTS, PLANTS, & MICROORGANISMS  
1964 — SOVIET VOSKHOD 1 WITH INSECTS, PLANTS, & MICROORGANISMS  
1965 — SOVIET VOSKHOD 2 WITH PLANTS, MICROORGANISMS, & TC  
1965 — MARCH — GEMINI 3 WITH HUMAN LEUKOCYTES AND SEA URCHIN EGGS

TABLE 7.— SPACE BIOLOGY — EARLY STUDIES (1966)

1966 — SOVIET KOSMOS 110 WITH DOGS, PLANTS, & MICROORGANISMS  
1966 — MARCH — GEMINI 8 WITH FROG EGGS  
1966 — JUNE — GEMINI 9 WITH MICROORGANISMS  
1966 — SEPTEMBER — GEMINI 11 WITH WHOLE HUMAN BLOOD & NEUROSPORA CRASSA SPORES  
1966 — NOVEMBER — GEMINI 12 WITH FROG EGGS AND MICROORGANISMS  
1966 — BIOSATELLITE I

TABLE 8.— SPACE BIOLOGY — EARLY STUDIES (1967–1969)

1967 — SOVIET KOSMOS 212 WITH TORTOISES & PLANTS  
1967 — SEPTEMBER — BIOSATELLITE II WITH WASP, FRUIT FLY, TRADESCANTIA & PLANT SEEDLINGS  
1968 — SOVIET ZOND 5 WITH TORTOISES, INSECTS, PLANTS, TC & MICROORGANISMS  
1969 — SOVIET ZOND 6 & 7 WITH TORTOISES, PLANTS & MICROORGANISMS  
1969 — SOVIET SOYUZS 5 & 7 WITH INSECTS, PLANTS & MICROORGANISMS  
1969 — JUNE — BIOSATELLITE III WITH PIGTAIL MONKEY ("BONNIE")

TABLE 9.— SPACE BIOLOGY — 1970 THROUGH 1971

1970 — SOVIET KOSMOS 368 WITH INSECTS, PLANTS, MICROORGANISMS & TC  
1970 — SOVIET ZOND 8 WITH PLANTS & MICROORGANISMS  
1970 — SOVIET SOYUZ 9 WITH PLANTS, MICROORGANISMS & FROG EGGS  
1970 — OFO-A ORBITAL VESTIBULAR EXPERIMENT WITH FROGS  
1971 — SOVIET SOYUZ-SALYUT WITH INSECTS, PLANTS, MICROORGANISMS & FROG EGGS



TABLE 10.— SPACE BIOLOGY — 1972 THROUGH 1973

1972 — APRIL — APOLLO 16 WITH MICROORGANISMS AND INVERTEBRATE & PLANT GAMETES

1972 — DECEMBER — APOLLO 17 WITH MICROORGANISMS, INVERTEBRATE & PLANT GAMETES AND POCKET MICE

1973 — MAY — SKYLAB 1/2 WITH MICROORGANISMS

1973 — JULY — SKYLAB 3 WITH FRUIT FLYS, POCKET MICE, HUMAN EMBRYO TC, FISH, SPIDERS, & SERUM PROTEINS

1973 — OCTOBER — SOVIET KOSMOS 605 WITH RATS & TORTOISES

1973 — NOVEMBER — SKYLAB 4 WITH PLANTS AND TC

TABLE 11.— U.S.S.R. BIOLOGIC EXPERIMENTS IN SPACE

	BALLISTIC FLIGHTS SEALED CABINS 1949-52	BALLISTIC FLIGHTS PRESSURE SUITS 1953-56	SUBORBITAL- TALKIN 1967	SPUTNIK 2 LAIKA 1957	SUBORBITAL 2 DOGS 1968	SUBORBITAL 1969	LAST SUBORBITAL 1960	1ST RECOVERED ORBITAL BELKA, STULKA SPUTNIK 4 1960	SPUTNIK V 1960	SPUTNIK VI 1961	SPUTNIK VII 1961	VOSTOK I AND II 1961	VOSTOK III TO VI 1962-63	VOSKOD I AND II 1964-65	KOSMOS 110 1966 VETEROK AND UGOKK	KOSMOS 212 1967	ZOND V TO VIII 1968-70	SOYUZ 5 TO 9 1969 TO 1970	SOYUZ SALGUT 1971	KOSMOS 606 1973
INSECTS								•	•	•	•	•	•	•			•	•	•	
CELLS, TISSUE CULTURE								•		•	•	•	•	•			•			
MICRO- ORGANISMS								•		•	•	•		•	•		•	•	•	•
PLANTS, SEEDS, CULTURE								•	•	•	•	•	•	•	•	•	•	•	•	•
GUINEA PIG										•										
RABBIT						•	•													
MICE, RATS								•		•	•									•
FROG, FROG EGGS										•								•	•	
TORTOISE																•	•			•
DOGS	•	•	•	•	•	•	•	•	•	•	•				•					
PRIMATES																				

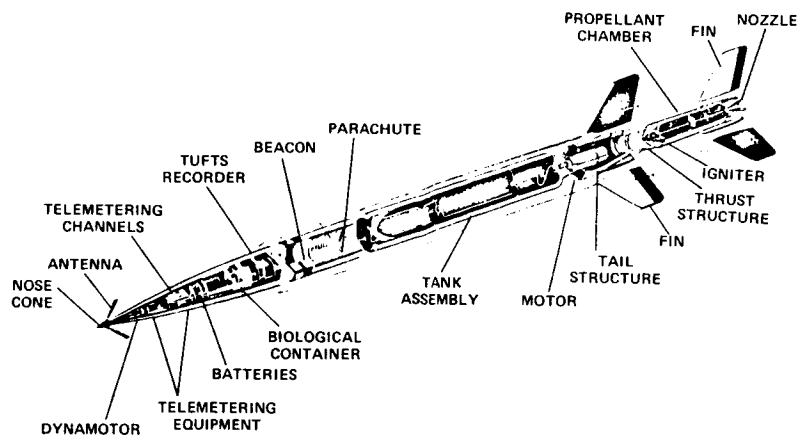


Figure 1.— Aerobee rocket.

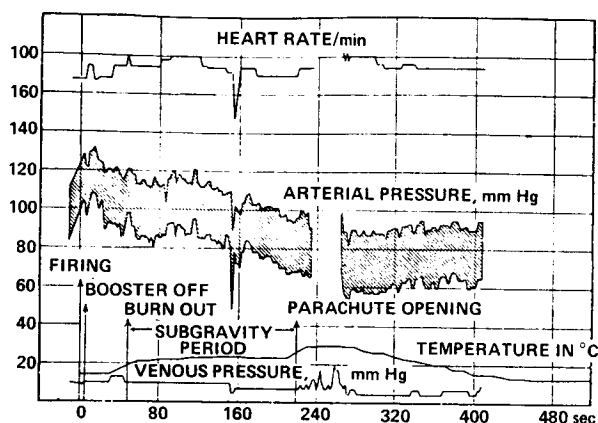


Figure 2.— Physiological data during Aerobee III rocket flight.

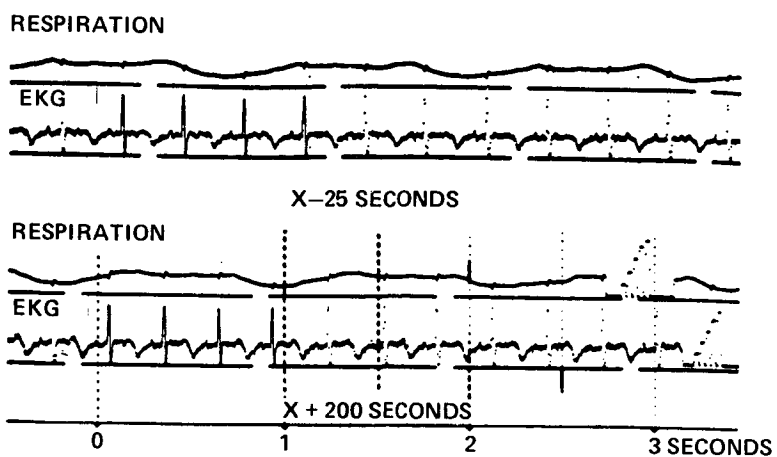


Figure 3.— ECG recordings from V-2 Aerobee III rocket flights.

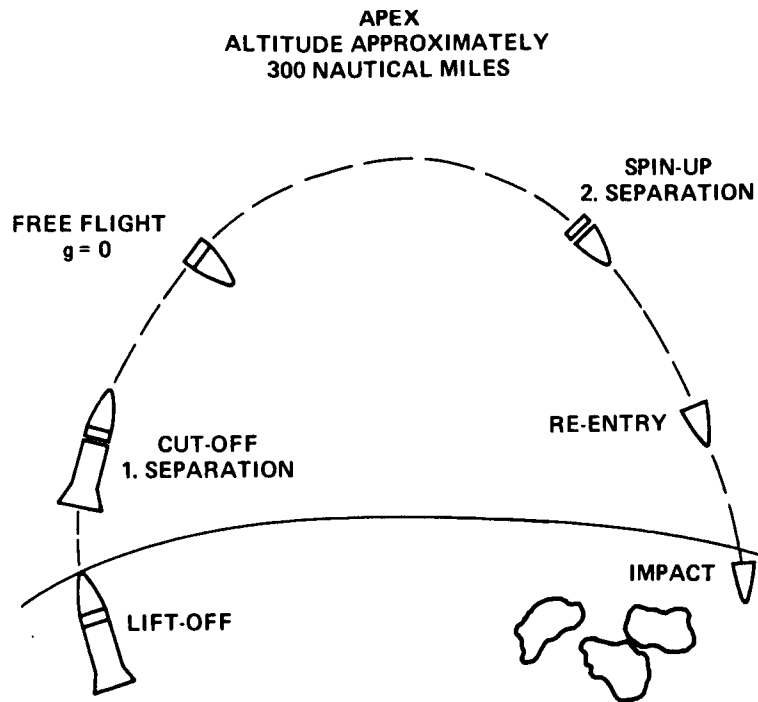


Figure 4.— Jupiter rocket trajectory.

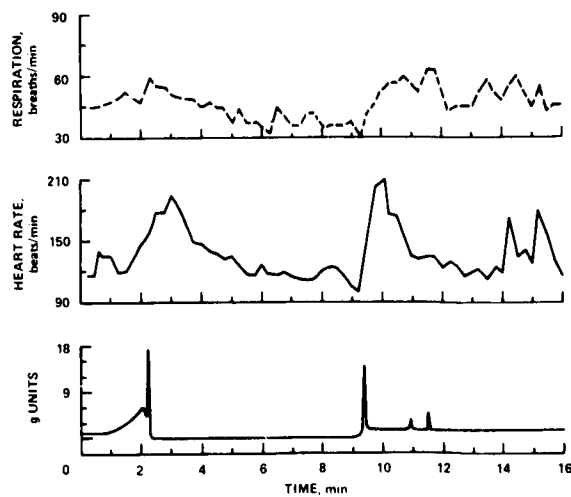


Figure 5.— The flight characteristics and recorded physiologic data from first chimpanzee flight MA-6.

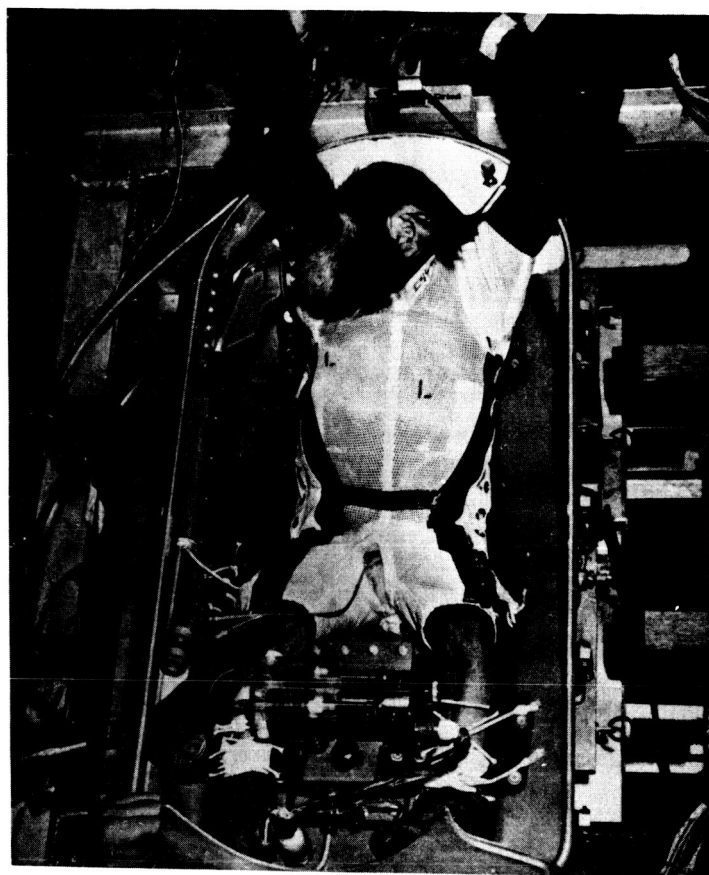


Figure 6.— Fully instrumented chimpanzee prior to orbital flight.

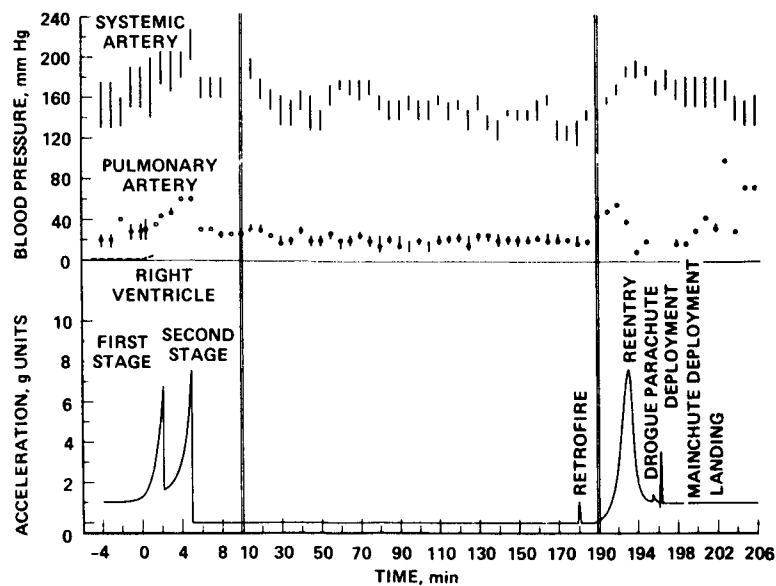


Figure 7.— Physiological data from MA-5 flight.

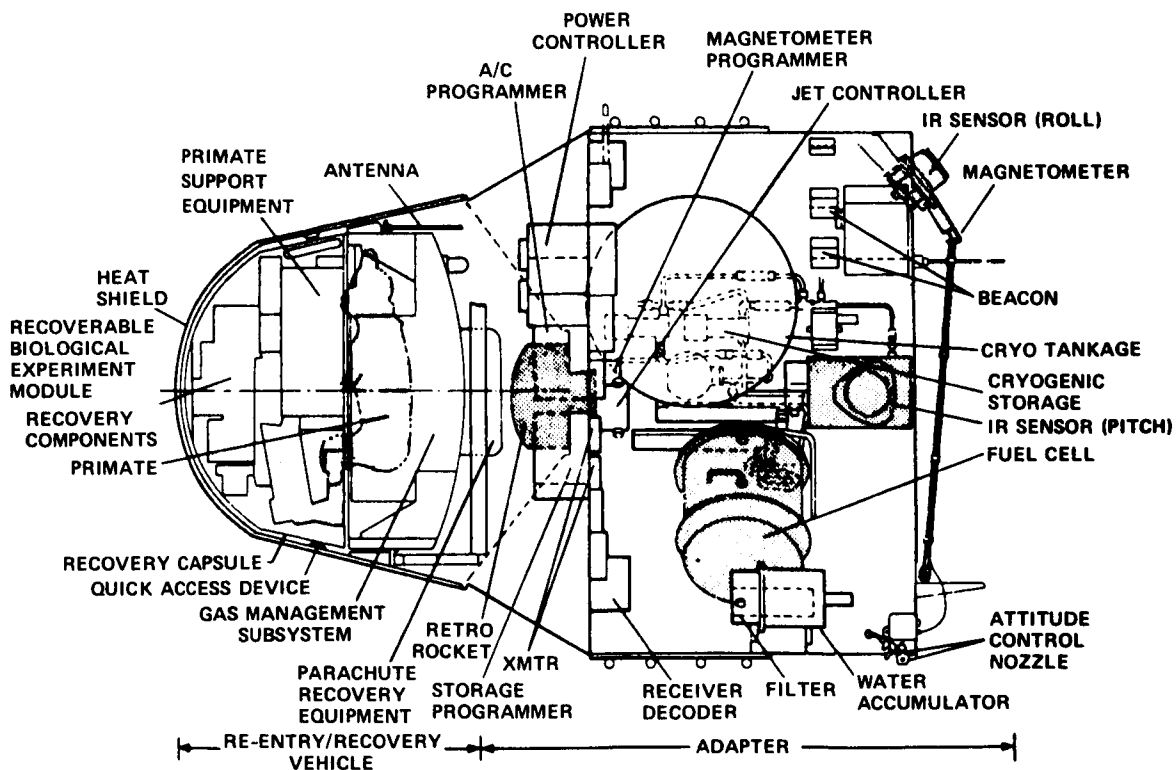


Figure 8.— Biosatellite III — cross section.

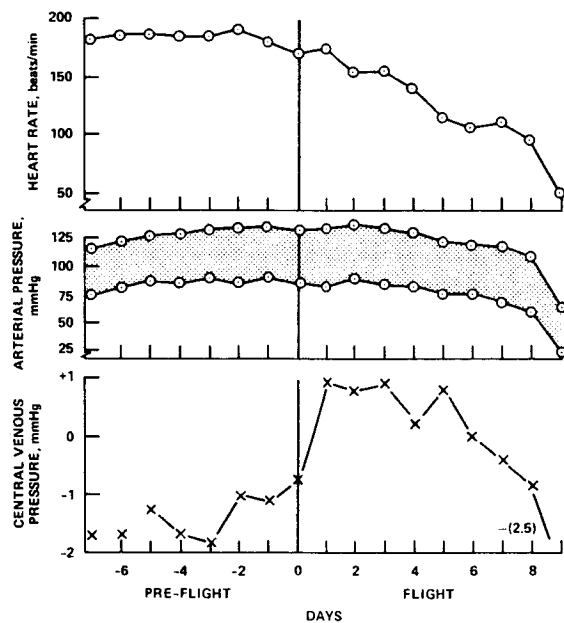


Figure 9.— Cardiovascular data – daily average of flight.

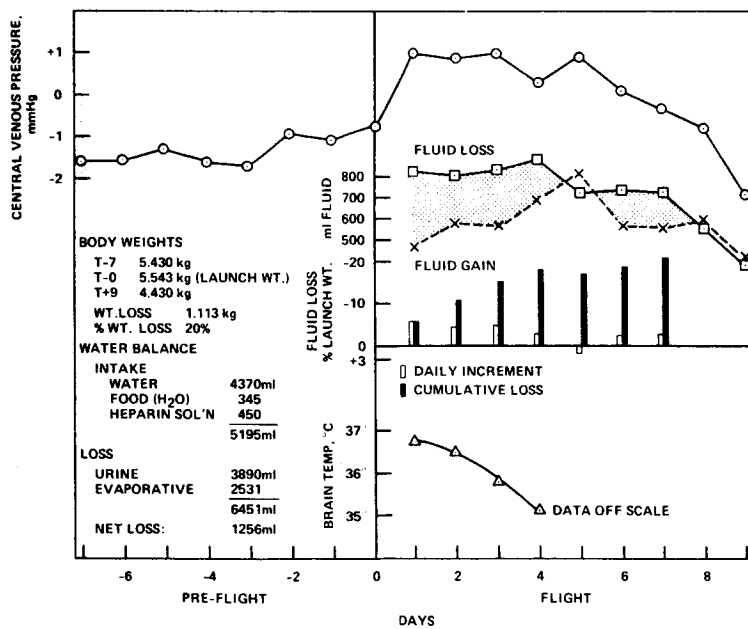


Figure 10.— Summary of fluid balance, body weight changes, and brain temperature, Biosatellite III.

# PHYSIOLOGICAL STUDIES IN SPACE WITH NONHUMAN PRIMATES USING THE MONKEY POD

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## INTRODUCTION

Man entered the Space Age with the historic 1.8-hr Earth-orbital USSR flight of Yuri Gagarin on 12 April 1961, an event that will be long remembered by the whole world. Less readily recalled are the Earth-orbital USSR flights of the seven instrumented dogs, starting with Layka in November 1957, during the months before Gagarin's great feat. The simple fact that these animals tolerated the exotic space environment well was regarded as a major milestone in the evolution of manned space flight, and few questioned the extrapolation of these animal experiments to man.

In analogous fashion, the chimpanzee Ham preceded Alan Shepard in the first USA Mercury suborbital flight, and Enos preceded John Glenn in the first Mercury Earth-orbital flight.

It is noteworthy, and even significant, that, much earlier, when man first left the ground to enter the Air Age in 1783, animals went first. Thus, in September of that year, the Montgolfier brothers launched their new invention, the hot-air balloon, for the edification of King Louis XVI at Versailles. Onboard were a sheep, a duck, and a rooster, all of which were recovered successfully. Thus, the first aerospace payload in history was a biological one. This flight was followed in less than a month by the first manned flight by J. F. Pilâtre de Rozier, and shortly thereafter, by many others.

With the brilliant successes of the manned spaceflight programs of both the USSR and USA during the past decade; an understandable apathy has prevailed concerning the study of space physiology through the use of experimental animals. A widely-held point of view, particularly in the USA, was that any physiological problems man might encounter in space were trivial, provided the hardware functioned reliably; hence, there was no need to study space physiology, other than secondarily, on the astronauts themselves. The drama of man landing on and exploring the Moon, of skillfully piloting a badly-disabled spacecraft back from 370,000 km (230,000 miles) out in space, and of repairing a severely damaged space station in orbit was manifestly much more evocative than for example, the physiological changes which might take place in the weightless state.

Yet, as all these dazzling accomplishments were occurring, there began to emerge a clear indication that subtle but fundamental and pervasive physiological changes do go on in man when he enters and remains in the weightless state for periods of time. Furthermore, as emerged at the SKYLAB Symposium in Houston last August, it is now evident that our current state of physiological knowledge, gleaned primarily in the 1-g Earth environment, is inadequate to explain the changes observed.

Quite apart from the obvious desirability of insuring the physiological well-being of the crews of future long-duration space flights, an understanding of the nature of the physiological changes

induced by weightlessness is also of basic importance to all of us who remain on Earth. It is only through a total grasp of human physiology that the manifold problems of medicine can be managed successfully.

Fortunately, the advent of the Space Shuttle Program promises a long-needed opportunity to the biomedical science community for making a rigorous research approach to the physiology of weightlessness. Not only can the studies on man himself be extended, but it will also be possible to use the powerful tool of animal experimentation on which so much physiological investigation depends.

The use of experimental animals provides several major advantages over the use of human subjects. Wide species differences among animals permit selection of particular specialized biological characteristics for study as appropriate. Animals can be maintained under constant nutritional and environmental conditions for long periods far more readily than can humans; in fact, experimental animals are frequently bred and raised under controlled conditions in the laboratory before use. Animals can be prepared with surgically implanted instrumentation of wide variety that would not be used in humans, either because of cosmetic disfigurement or because of risk to life. Environmental and nutritional variables can be systematically manipulated over a wider range with animals than would be desirable or permissible with humans. Organs can be partially or wholly extirpated in animal experiments. When necessary, animals can be sacrificed in the course of experiments to provide essential information.

While data from animal experiments can never wholly supplant direct observations on man, at the same time, the use of experimental animals provides physiological insights difficult or impossible to obtain through the exclusive use of human subjects. It is thus the complementary approach of both human and animal experimentation that permits meaningful advance in basic physiological knowledge and the solution of practical medical problems.

Several years ago, on the basis of selection criteria to be discussed in a subsequent paper, our laboratory chose the subhuman primate *Macaca nemestrina*, also known as the pig-tailed monkey or giant rhesus, as an optimal experimental animal in which to investigate the physiological effects of the weightlessness of space flight. However, regardless of the animal species selected, the first requirement for any scientifically valid animal experiment is that the results obtained from manipulation of the experimental variables be compared with results of the same measurements made on animals kept under the same total conditions as the experimental subjects, except for the change in the particular variables being studied.

With this requirement in mind, an essential first step in the use of animals to study the physiological effects of weightlessness is the definition of the appropriate control conditions for such experiments. Ideally, the control conditions should be such that the animal can be maintained in a reproducibly stable and good physiological state, without the imposition of the experimental variables, while the desired measurements are being carried out. Thus, theoretically, when the experimental variable is imposed under the same conditions, any difference in the measured results can be ascribed to it alone.

As a secondary but still important consideration, many physiological measurements require that a physical connection be made between the animal and instrumentation or apparatus. Also, the



acceleration profiles involved in spacecraft launch and reentry procedures dictate some form of restraint for animal subjects, just as for human passengers.

There are undoubtedly numerous ways in which these basic requirements can be met for animal experimentation on the effects of weightlessness. However, it is evident that the special characteristics of weightlessness, as achieved through space flight, preclude the simple transfer of ordinary laboratory procedures to animal studies in this environment.

Accordingly, we undertook the design and fabrication of a system that permits the continuous maintenance of an unanesthetized, adult, 10-12 kg (25 lb) monkey in a physiologically stable state of comfortable restraint for periods of at least 10 days, either on the ground or in an orbiting spacecraft. The system had to provide appropriate atmospheric and thermal conditions, adequate food and water, and a means for excreta management. It was also deemed important to make provisions for the application of a standardized provocative physiological test, such as the lower-body negative pressure test, to the animal at intervals as desired. In our view, these constitute an irreducible minimum set of requirements for the class of experiments in which we are interested.

Historically, the first step we took was the fabrication of a fiberglass couch and nylon-net restraint jacket combination, shown in figure 1, which approximated the geometrical configuration of the Mercury astronaut couch. After numerous small but critical modifications, primarily the addition of a footbar to avoid dependent edema and the addition of lucite bars to the couch seat to form the actual points of contact, we were able to maintain a 10-kg pig-tailed monkey successfully for 90 days of continuous restraint in this configuration.

The side rails on the couch were designed to permit the assembly to slip into tracks mounted on the inside of a 55-gal steel drum, as shown in figure 2. The drum could be sealed, and ventilated with a stream of fresh air for several hours at a time. The exhaust gas could be monitored for  $O_2$  and  $CO_2$  partial pressures, and, from these measurements, the metabolic rate of the animal could be computed. Chronically implanted vascular catheters permitted continuous heart-rate and blood-pressure recordings to be made. Reports on these techniques and basic physiological parameters measured in *Macaca nemestrina* were published from our laboratory in 1964 (refs. 1 and 2).

Out of these early developments, there emerged the concept of a completely enclosed module in which a monkey could be maintained in comfortable restraint for days at a time while physiological data were being recorded. The design of the module was to incorporate the features necessary to permit experimentation in the spacecraft environment, as well as on the ground. Accordingly, NASA funded a feasibility study effort by our laboratory of what was termed the "Automated Primate Research Laboratory" (APRL) concept, which culminated in a final report published in 1972 (ref. 3).

The report summarized a wealth of detail on the physiological characteristics of *Macaca nemestrina*, on a variety of engineering concepts for development of a suitable system, and even on a management plan for implementing construction. However, the decreased availability of funding for such projects within NASA precluded the approach suggested. Accordingly, a much more modest approach has been in progress in our laboratory during the past 3 years, which has resulted in the monkey-pod system described herein. A preliminary description was presented at the 1973 meeting of the Committee on Space Research (COSPAR) (ref. 4).

## APPARATUS

The basic element is a lightweight fiberglass pod and couch assembly, shown in figure 3. It is approximately 90 cm high by 60 cm wide by 70 cm deep, and weighs 30 kg without a monkey. The component parts of the assembly are shown in figure 4.

It may be seen that the outer shell or pod is formed by an upper half and a lower half, which are joined by a circular O-ring seal so that the entire pod is gas tight. A nylon-net restraint jacket forms an integral part of a fiberglass couch, so that a monkey can be seated in the couch and held in place by the jacket, but with considerable freedom of motion. The seat and lower back of the couch are padded with a viscoelastic matrix covered with silicone rubber, and are provided with holes to permit the urine and feces excreted by the animal to pass into the space below the seat. The foot platform of the couch is provided with a footbar, which can be grasped at will by the animal and which is essential for the prevention of dependent edema when an animal remains in the couch for more than a day or two. Two sets of loose leg shackles, one across the upper legs and one across the lower legs, complete the restraint system. These permit relatively free side motion of the limbs but limit straightening.

A single-piece silicone rubber bellyband and skirt is put on the monkey to provide a gas seal between the upper and lower halves of the pod, so that each half can be ventilated independently. This is placed below the skirt of the nylon-net jacket and above a set of rigid plates arranged in such a way as to provide mechanical support for the silicone rubber seal when a negative pressure differential is created in the lower pod. The rigid plates are designed to slide freely on each other so as to allow for lateral movement of the animal in the seat.

The waist seal is a major feature of the monkey-pod system. By allowing the independent ventilation of the upper half of the animal, not only is the respiratory gas exchange measured more accurately by virtue of the reduced dead-space of the pod but also the animal is spared respiring gaseous emanations from his excreta. Conversely, the excreta produced by the animal are confined to the lower half of the pod, making quantitative recovery easier. Finally, the waist seal permits the application of as much as 80 torr of lower-body negative pressure to the animal as desired.

## PROCEDURE

In practice, the animal is installed in the couch outside of the pod, and then the animal in the couch can be inserted readily into the lower half of the pod, where the couch is latched into place at fixed suspension points. The lower half of the pod is lined with sheets of ashless filter paper to soak up excreta produced by the animal. These serve to aid the evaporation of water from the excreta during a test, and to aid in the quantitative recovery of the excreta at the end of the test. When a test is finished, the couch is lifted part way out of the pod, and the animal and couch surfaces are carefully rinsed with distilled water into the pod before complete removal of the couch.

The contents of the pod, including the filter-paper lining, are transferred quantitatively to a drying tray and placed in a lyophilizer. The dried material is weighed and extracted with petroleum ether to determine fat content. The dried, defatted excreta plus filter paper are finely comminuted

in a Wiley mill and thoroughly mixed. Aliquots are then digested or ashed appropriately for measurement of the nine elements: nitrogen, calcium, phosphorus, potassium, sodium, magnesium, chlorine, sulfur, and iron.

Four-day collection periods have been found to be convenient for metabolic balance studies, although the duration can readily be varied from 1 to 10 days. Consecutive collection periods are also entirely feasible.

With the upper half of the pod in place, a constant inflow of fresh air at a rate of 8 liters/min is sufficient to maintain a  $P_{I\text{O}_2}$  of approximately 150 torr and a  $P_{I\text{CO}_2}$  of 6 torr, as well as to provide for removal of water evaporating from the upper part of the animal. By measuring volume flow, pressure and temperature of the exhaust gas together with  $P_{\text{O}_2}$ ,  $P_{\text{CO}_2}$ ,  $P_{\text{N}_2}$  and  $P_{\text{H}_2\text{O}}$ , it is possible to compute the respiratory gas exchange of the animal.

The upper pod also incorporates a simple food-tablet dispenser which is operated *ad libitum* by the monkey through manipulation of a spring-loaded handle. If desirable, more elaborate performance-task feeders can be used. An *ad libitum* automatic water-dispenser nozzle, which is activated by 10 torr of oral suction, is also provided within the upper pod. These devices permit continuous recording of feeding and drinking activity, as well as accurate measurement of food and water intake during an experiment. The food-tablet and drinking-water reservoirs are outside the pod, and are readily accessible for content replenishment at any time.

The food tablets used in our laboratory are manufactured commercially. The nearly spherical tablets are 1 cm in diameter and have a mean weight of 0.79 g. Their nutritional characteristics are shown in table 1. It may be noted that the tablet formulation is exceptionally high in protein content, and quite high in calcium content. While this is quite acceptable to the monkeys, it would be desirable to reduce the content of both of these constituents for metabolic balance studies to improve their accuracy.

During 1973, NASA made available to our laboratory one of the SKYLAB respiratory-gas mass spectrometers developed by the Perkin-Elmer Company of Pomona, California. The instrument is a duplicate of the one still in orbit in SKYLAB, and which was used successfully by the astronauts in the exercise tolerance tests during all three flight missions. It is designed to measure  $P_{\text{N}_2}$ ,  $P_{\text{O}_2}$ ,  $P_{\text{CO}_2}$  and  $P_{\text{H}_2\text{O}}$  continuously and simultaneously by means of four fixed ion-collectors, and we have adapted it to make these measurements on the exhaust gas from the upper half of the monkey pod. Table 2 gives typical values obtained during two monkey pod trials, and shows the sensitivity and accuracy of the instrument. It may be seen that the summation of the individual measured gas partial pressures closely approximates the independently measured total barometric pressure, in accordance with Dalton's Law. The slight discrepancy between the two values is assumed to be due largely to the unmeasured argon content of the air, which is of the order of 6 to 7 torr under these conditions.

So far, we have made 18 pod runs of 2 to 10 days duration on seven different monkeys in order to test the compatibility of the animals with the pod system. In all of these runs, the food and water intakes were recorded, and the body weight of each animal was measured before and after the run, as shown in table 3. It may be seen that, in general, the animals ate, drank, and maintained body weight quite well. The monkeys also tolerated these pod tests very well by visual criteria:

there was little indication of struggling, the animals remained alert, and there was no evidence of major skin abrasions or irritation. Thus, we conclude that pod runs of at least 10 days duration pose no practical problems. As opportunity permits, we plan a systematic extension of pod residence periods in order to establish the ultimate limits on the system.

It should be noted that the physical problems posed by this kind of restraint are probably more severe on the ground than they are likely to be in the weightless state, especially in these large animals, primarily because of the continual threat of contact-pressure ischemia if the animals sit too long in one spot without moving. However, it is worth reiterating that, in our earlier couch-restraint studies, we had one animal which went 90 days continuously, and others which have gone for 30 days.

## RESULTS AND DISCUSSION

We shall now turn to a consideration of some of the physiological data we have been able to obtain by means of the monkey-pod system shown in figure 5. Table 4 shows the energy balance determinations that were made during three different tests, each lasting 4 to 5 days. One was a test of 4.1 days in our laboratory, the second was the 4.1-day Shuttle Concept Verification Test II (CVT-II) conducted at the Ames Research Center in April 1974 (ref. 5), and the third was the 5.0-day Shuttle Concept Verification Test III (CVT-III) conducted at the Marshall Space Flight Center in July 1974 (ref. 6).

In the first test, the animal gained almost 600 g of body weight during the 4.1-day period. At the same time, he took in more food calories than the metabolic energy he released as computed from his total  $O_2$  consumption. Thus, he was in positive energy balance.

In the Shuttle CVT-II, the animal lost about 700 g of body weight during the 4.1-day period. In this case, he took in fewer food calories than the metabolic energy he released; hence, he was in negative energy balance.

In the Shuttle CVT-III, however, the results were anomalous. While the animal's body weight did not change appreciably in the course of the 5 days involved, he seemed to be in a substantial positive energy balance during this period. From the data in table 4, it is clear that the  $O_2$  consumption rate and  $CO_2$  production rate were both closely comparable with those measured in the two previous tests. On the other hand, his food intake was markedly higher, so that he should have gained body weight. A possible explanation for this apparent anomaly is that the animal may not have taken in as much water as he might during this period, resulting in a corresponding body-weight deficit. Water balance measurements would have settled this point. They were not carried out during these tests, but technically they are quite feasible with the basic pod design.

Table 5 summarizes the nominal matter and energy balance to be expected during pod tests with 11- to 12-kg pig-tailed monkeys; these tests were conducted to provide data for engineering planning in spacecraft applications. An interesting feature of this tabulation is that the latent heat loss by evaporation of all the water lost by the animal is actually greater than the metabolic heat production during the same period. Thus, if all the water liberated into the pod by the animal were

to be evaporated, the exhaust gas temperature could be expected to be cooler than the inlet gas temperature.

The manpower resources of our laboratory have allowed us to complete the biochemical analyses for only a very small number of elemental balance studies with the pod, although we now have all of the requisite analytical procedures for nine elements well in hand. Table 6 contains the results from a 4.1-day pod experiment performed some time ago, before all of the analytical procedures were completely developed; hence, these data should be viewed as being illustrative rather than definitive.

The intake for each element was computed from the total weight of food ingested and the food composition data shown earlier in table 1. The excretion for each element was determined by analysis of the contents of the lower pod as described earlier. For six of the elements, the animal seemed to be essentially in zero balance for the 4.1-day period. However, the results indicate an apparent positive balance for nitrogen, phosphorus, and iron.

In the case of nitrogen, there is growing evidence that a significant fraction of the body turnover may involve loss through conversion of amino nitrogen to  $N_2$ , especially on excessively high protein diets such as the present one. Thus, estimation of nitrogen balance without taking this into account would indicate an apparent positive nitrogen balance. Another possible source of error might be the conversion of significant quantities of excreta amino nitrogen to ammonia by bacterial decomposition in the course of several days. However, we have quantitatively collected the ammonia appearing in the lower-pod ventilating air, and, after 4 days, less than 1 percent of the nitrogen turnover would be accounted for in this form. It appears, as stated earlier, that a diet formulation containing substantially less protein would provide a considerable advantage for assessing nitrogen balance in such studies, yet continue to supply the minimum daily requirement of essential amino acids.

The most likely explanation for the apparent positive phosphorus and iron balances in this particular experiment was probably analytical artifact. We feel that this problem has now been corrected, but further analytical results are needed to decide the matter. In broad terms, however, it is now evident that the monkey-pod system is well suited to carry out experiments in which it is desired to measure material and energy balances, especially in the space environment.

The system also makes it possible to measure cardiovascular function parameters continuously in the pod animal. For example, it is a relatively simple matter to apply skin ECG electrodes to the torso of the monkey underneath the nylon-net restraint jacket, and lead the wires out through the back of the pod to a cardiometer for continuous monitoring and recording of heart rate.

Figure 6 shows a plot of the mean hourly heart rate of a 12-kg *Macaca nemestrina* during a 10-day pod experiment. It may be seen that the heart rate showed a strong diurnal cycle, and remained quite stable for the duration of the experiment. The mean heart rate for the entire 10-day period was 142 beats/min, during the 12-hr light period, the mean heart rate was 152 beats/min, and during the 12-hr dark period, it was 133 beats/min.

Figure 7 gives results obtained on the *Macaca nemestrina* subject of the monkey-pod experiment during the Shuttle CVT-III at the Marshall Space Flight Center. Plotted in the upper part of

the graph are duplicate 24-hr cycles of the mean  $O_2$  consumption and  $CO_2$  production rates for each hour of the day during the 5-day test. The mean heart rate for each hour of the day is shown in the lower part of the graph. It may be seen that there is excellent correlation between these three independently measured parameters, indicating that heart rate is probably indicative of level of physical activity in this test. It is noteworthy that there is a tendency for the respiratory gas exchange to lag slightly behind the changes in heart rate, but how much of this is physiological and how much is gas sampling lag time remains to be determined.

As mentioned earlier, our original couch design was based on that of the Mercury astronaut couch, so that animals could be positioned optimally to withstand launch accelerative forces simply by tipping the couch backward to the supine position before launch. This design feature also permitted Mr. Richard C. Mains of our laboratory to make a study of the cardiovascular responses to lower-body negative pressure (LBNP) in supine monkeys. The apparatus he devised is shown in figure 8, and represents the forerunner of the system now incorporated into the lower part of the monkey pod.

It was found that, after training, our pig-tailed monkeys could be placed in the supine position in the couch and their resting heart rate would stabilize within a few minutes. Figure 9 shows the mean heart rate response of five *Macaca nemestrina* in the supine position to the application for 5 min of each of three increasing levels of LBNP, 40, 50, and 60 torr, followed by the release of the LBNP. It may be seen that LBNP produces a tachycardia similar to that observed in man, and that the level of tachycardia is proportional to the degree of LBNP imposed. Recovery of the heart rate is fairly prompt on release of the LBNP.

While it is clear that *Macaca nemestrina* shows a tachycardia in response to the application of LBNP, it is important to establish the equivalence of this response to that seen in man under comparable conditions. It is also of interest to compare the level of equivalence between LBNP and passive tilt to the vertical from the supine position in producing tachycardia.

Accordingly, a series of experiments was performed in which the heart rate response of five *Macaca nemestrina* to 40 torr of LBNP for 15 min was compared to that in the same animals when they were tilted  $90^\circ$  to the vertical position for 15 min and then returned to the supine position. The results are plotted in the middle graph of figure 10, and it may be seen that the two sets of responses are very similar and statistically indistinguishable. There is a suggestion in the data that heart rate recovery after LBNP is more rapid than that after tilt, but this was not statistically demonstrable.

The lower graph in figure 10 contains data from the paper of Musgrave *et al.* (ref. 7) in which the mean heart rate response of five men to 40 torr of LBNP for 15 min was compared in the same subjects with their heart rate response to a  $70^\circ$  passive tilt to the near-vertical for 15 min before returning to the supine position. As may be seen, the two sets of responses were quite similar, and these authors concluded that LBNP and passive tilt to the vertical produced generally equivalent responses. Again, as in the case in the monkey data, there is a suggestion that heart rate recovery after LBNP is more rapid than that after tilt.

The adaptability of *Macaca nemestrina* to the supine position in the couch permitted us to examine the effects of prolonged periods of recumbency on cardiovascular function. Two monkeys, which had been prepared several weeks earlier with chronically indwelling vascular catheters in the

ascending aorta and the pulmonary artery (ref. 8), were placed in continuous supine couch restraint for 14 days in the LBNP apparatus shown earlier in figure 8. The animals were subjected to 15 min of 40 torr LBNP on day 1, day 7 and day 14 of the recumbency period, and the cardiovascular data obtained during the three LBNP tests are plotted in figure 11.

The second graph from the top in figure 11 shows the change in heart rate from the mean heart rate determined for 15 min before application of LBNP for each of the two animals. It may be seen that, as the recumbency continued, the heart rate response to 40-torr LBNP was progressively increased in both animals. Furthermore, in one of the animals, #362, the LBNP on day 14 of recumbency had to be terminated after 10 min because the mean aortic pressure had fallen to 50 torr and the animal began to show signs of syncope.

The middle graphs in figure 11 indicate the changes in mean aortic pressure from the baseline values during and after application of LBNP. In animal #404, there was indication that the fall in pressure at the 14th minute of LBNP was greater after 1 and 2 weeks of continuous recumbency than at the start. In the other animal, #362, 15 min of LBNP seemed to have no effect on mean aortic pressure through the first week of recumbency, but, by the end of the second week, only 10 min of LBNP produced a profound fall in mean aortic pressure. Thus, it might be concluded that animal #404 tolerated 14 days of continuous recumbency better than did animal #362.

The behavior of the aortic pulse pressure in the two animals is shown in the second graphs from the bottom in figure 11. It may be seen that in animal #404 there was a consistent drop of 15 to 20 torr in pulse pressure with the application of LBNP throughout the 2-week of recumbency. In the case of animal #362, the pulse pressure change during LBNP on day 7 of recumbency could not be computed because of damping of the aortic pressure tracing at that time. However, it is apparent that the pulse pressure was maintained during LBNP on day 1 of recumbency, whereas it fell off during LBNP on day 14 of recumbency.

The values for mean pulmonary pressure during LBNP in the two monkeys are plotted in the bottom graphs of figure 11. There was a consistent drop of 3 to 5 torr with the application of LBNP, which was immediately reversed at the release of LBNP, and which did not seem to change with prolonged recumbency. The decrease in mean pulmonary pressure with the onset of LBNP measured in these monkeys agrees with the data of Bevegård *et al.* (ref. 9) in human subjects. They measured mean pulmonary artery pressure in 10 men in the supine and sitting positions, and found that, on the average, it was 4 torr lower in the sitting position than in the supine.

The data from these monkey recumbency experiments can be compared with the measurements of Menninger *et al.* (ref. 10) on two men after 2 weeks of bed rest. In their study, the heart rate response to the application of 40 torr of LBNP for 5 min was recorded at the start and at the end of the 14-day period of recumbency. In figure 12, the increase in heart rate response to 40 torr LBNP on day 14 of recumbency over the heart rate response at the start of recumbency is shown for our two monkey subjects and for the two human subjects of Menninger *et al.*; it may be seen that the changes are very similar.

Although the monkey pod is designed to permit application of LBNP in the course of experiments, time has not yet permitted us to carry out recumbency studies with the pod system. However, it was possible to try out the LBNP procedure during the two Shuttle Concept

Verification Tests in which we recently participated. In these trials, 20 torr of LBNP were administered for 15 min once a day during both tests with the monkey in the upright seated position; hence, the results are not directly comparable to the other data we have presented. Figure 13 shows the heart rate values obtained during the LBNP procedures administered in the course of the Shuttle CVT/GPL III at the Marshall Space Flight Center last July, and are of interest primarily for demonstrating the feasibility of utilizing LBNP in monkey-pod experiments.

## CONCLUSIONS

On the basis of the results presented here, it is reasonable to conclude that *Macaca nemestrina* responds to prolonged recumbency in the supine position in much the same way as man, insofar as change in cardiovascular function is concerned. It is also reasonable to conclude that the application of LBNP to *Macaca nemestrina* constitutes a valid provocative test of cardiovascular function, just as it does for man. Therefore, since prolonged recumbency evokes many of the physiological changes that occur during exposure to weightlessness, it appears that *Macaca nemestrina* is a valid and good animal model for man in the study of the physiology of weightlessness.

The development of the monkey pod in our laboratory has provided a practical modular experiment system which permits the physiological study of adult, 10- to 12-kg primates maintained in the same microenvironment on the ground and in orbiting spacecraft. The design of the pod also makes possible the application of a wide variety of measuring instruments, techniques, and procedures, so that rigorously quantitative physiological data may be obtained. The pod has been used successfully for ground experiments lasting 10 days, with no detectable compromise of the physiological well-being of the animal, and there is good indication that this period can be lengthened twofold to threefold.

Currently, work in our laboratory is being directed at the development of a two-pod system in which the major instrumentation can be shared between two monkeys by appropriate commutation procedures. The basic arrangement is shown in figure 14, and it is this arrangement that we consider to be practical for space-flight experiments. The time constants of the physiological parameters being measured are such that it is entirely feasible, for example, to utilize the respiratory gas-analysis system for the two pods simply by commutating the gas sampling. The ability of make measurements on two or more animals with one set of instrumentation is not only cost-effective, but it improves the statistical base for the experiments themselves. If desired, it also permits an experiment design in which the animal in one pod can serve as a control for the animal in the second pod. Thus, we deem it of basic importance to demonstrate the feasibility of carrying out multiple-pod experiments.

Although our laboratory has a primary interest in conducting studies on the physiology of weightlessness through space-flight experiments, and has developed the monkey-pod system to help achieve that goal, the system is also of potential use to other experimenters. We prefer *Macaca nemestrina* as our animal model, but the pod system is equally useful for experiments involving other macaques such as *Macaca mulatta*. Additionally, with appropriate modification, it could be used with other primates, and many of the principles involved applied to nonprimate species, as well.



It should be emphasized that, whatever animal species is used in physiological experimentation, the results are only as good as the adequacy of the controls. The monkey-pod system described here represents a practical means for meeting this fundamental scientific requirement under the special conditions of space flight.

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TABLE 1.— NUTRITIONAL CHARACTERISTICS OF 100 g OF  
THE FOOD TABLETS SUPPLIED TO THE MONKEYS

Constituent	Weight (g)	Caloric value (kcal)	Metabolic water (g)
Carbohydrate	60.8	243	36.5
Protein	22.0	88	8.4
Fat	2.0	18	2.1
Water	8.0	0	.0
Fiber	3.0	0	.0
Minerals	4.2	0	.0
Total	100.0	349	47.0
Nitrogen	3.52		
Calcium	.902		
Potassium	.704		
Phosphorus	.506		
Chlorine	.466		
Sodium	.223		
Magnesium	.143		
Sulfur	.0578		
Iron	.0326		
Mean tablet weight is 0.79 g			

TABLE 2.— MEAN VALUES FOR MONKEY-POD GAS CHARACTERISTICS DURING  
TWO TRIALS OF 4.1 AND 5.0 DAYS DURATION ON *Macaca nemestrina*

Gas characteristics	#337, Simple ARC/CVT-II		#337, Simple MSFC/CVT-III	
	Cabin air	Upper-pod gas	Cabin air	Upper-pod gas
Pod gas flow (liters/min)	8.45	8.45	7.91	7.91
Ambient gas temperature (°C)	21.6	28.2	22.1	24.2
Relative humidity (%)	25	46	43	75
Ambient barometric pressure (torr)	763.3	763.3	747.9	747.9
Gas partial pressure ( $P_g$ )				
$P_{N_2}$ (torr)	593.8	589.0	580.7	576.6
$P_{O_2}$ (torr)	158.2	150.1	155.4	146.9
$P_{CO_2}$ (torr)	.0	5.7	.0	7.1
$P_{H_2O}$ (torr)	4.8	13.1	8.5	17.0
$\Sigma P_g$ (torr)	756.8	757.9	744.6	747.6
$P_B - \Sigma P_g$ (torr)	6.5	5.4	3.3	.2
Gas fractional composition				
$N_2$ (%)	77.79	77.16	77.64	77.10
$O_2$ (%)	20.73	19.66	20.78	19.64
$CO_2$ (%)	.03	.75	.03	.95
$H_2O$ (%)	.63	1.72	1.14	2.27
$\Sigma$ (%)	99.18	99.29	99.59	99.96

TABLE 3.— POD TRIALS ON SEVEN *Macaca nemestrina* MONKEYS

Monkey no.	Time in pod (d)	Body weight			Food intake (g/24 hr)	Water intake (g/24 hr)
		Start (kg)	End (kg)	Change (g/24 hr)		
50	2.0	11.96	11.41	- 275	58	0.64
174	3.0	10.88	11.42	+ 270	243	1.18
341	3.2	11.61	11.65	+ 13	296	1.15
337	3.8	10.60	11.17	+ 150	186	1.12
337	4.0	11.30	10.94	- 90	231	1.40
337	4.1	11.55	12.15	+ 146	216	1.22
337	4.1	12.41	11.70	- 173	108	.98
307	4.1	11.54	12.12	+ 58	154	.79
337	5.0	11.00	10.96	- 8	200	1.05
337	5.1	11.75	11.28	- 92	90	.82
341	6.9	12.15	11.30	- 123	206	2.24
290	7.0	12.18	11.57	- 87	45	.44
337	8.2	11.00	10.38	- 76	211	1.07
307	9.0	11.90	11.23	- 74	153	.75
337	10.0	10.70	11.43	+ 73	235	1.06
411	10.0	10.38	9.85	- 53	64	.36
341	10.0	11.92	12.11	+ 19	179	1.09
307	10.1	11.96	11.61	- 35	171	.72
Mean	6.1	11.49	11.35	- 20	169	1.00
N = 18						

TABLE 4.— ENERGY BALANCE COMPUTATION FOR THREE MONKEY-POD  
TRIALS WITH *Macaca nemestrina*

	EPL test	ARC CVT-II	MSFC CVT-III	Mean
Monkey no.	307	337	337	
Time in pod (d)	4.1	4.1	5.0	
Start body weight (kg)	11.54	12.41	11.00	
End body weight (kg)	12.12	11.70	10.96	
Body weight change (kg)	+ .58	- .71	- .04	
Water intake (liters)	3.24	4.00	5.25	
Food intake (g)	631	442	1,001	
Caloric intake (kcal)	2,202	1,543	3,493	
CO <sub>2</sub> produced (liters)	394	335	458	
O <sub>2</sub> consumed (liters)	434	388	535	
Caloric output (kcal)	2,105	1,882	2,595	
Caloric balance (kcal)	+97	-339	+898	
<hr/>				
Water intake (liters/24 hr)	0.79	0.98	1.05	0.94
Food intake (g/24 hr)	154	108	200	154
CO <sub>2</sub> production (liters/24 hr)	96	82	92	90
O <sub>2</sub> consumption (liters/24 hr)	106	95	107	103
Respiratory quotient	.91	.86	.86	.88
Caloric intake (kcal/24 hr)	537	377	698	537
Caloric output (kcal/24 hr)	513	459	519	497
Caloric balance (kcal/24 hr)	+24	-82	+179	+40

TABLE 5.— NOMINAL MATTER AND ENERGY BALANCE  
FOR THE MONKEY POD CONTAINING  
A 10 TO 12 kg *Macaca nemestrina*

Input to monkey	
Water (liters/24 hr)	1.0
Food (g/24 hr)	200
Oxygen (liters/24 hr)	100
Output from monkey	
Water (liters/24 hr)	1.1
Carbon dioxide (liters/24 hr)	90
Metabolic heat (kcal/24 hr)	500
Pod air supply (dry, 25°C)	
Upper pod (liters/min)	10
Lower pod (liters/min)	25
Latent heat loss	
Water evaporation (kcal/24 hr)	640

TABLE 6.— METABOLIC BALANCES FOR NINE ELEMENTS DURING  
A 4.1-DAY POD TRIAL WITH *Macaca nemestrina*

Element	Intake (g)	Excreted (g)	Net retention (+) or loss (-) (g)
Nitrogen	22.2	18.2	+4.0
Calcium	5.69	5.46	+ .23
Potassium	4.44	4.58	- .14
Phosphorus	3.19	2.33	+ .86
Chlorine	2.94	2.82	+ .12
Sodium	1.41	1.56	- .15
Magnesium	.902	.782	+ .12
Sulfur	.365	.348	+ .017
Iron	.206	.127	+ .079
Total food ingested = 631 g			
Excreta dry weight = 105 g			
Excreta fat content = 2.5 g			

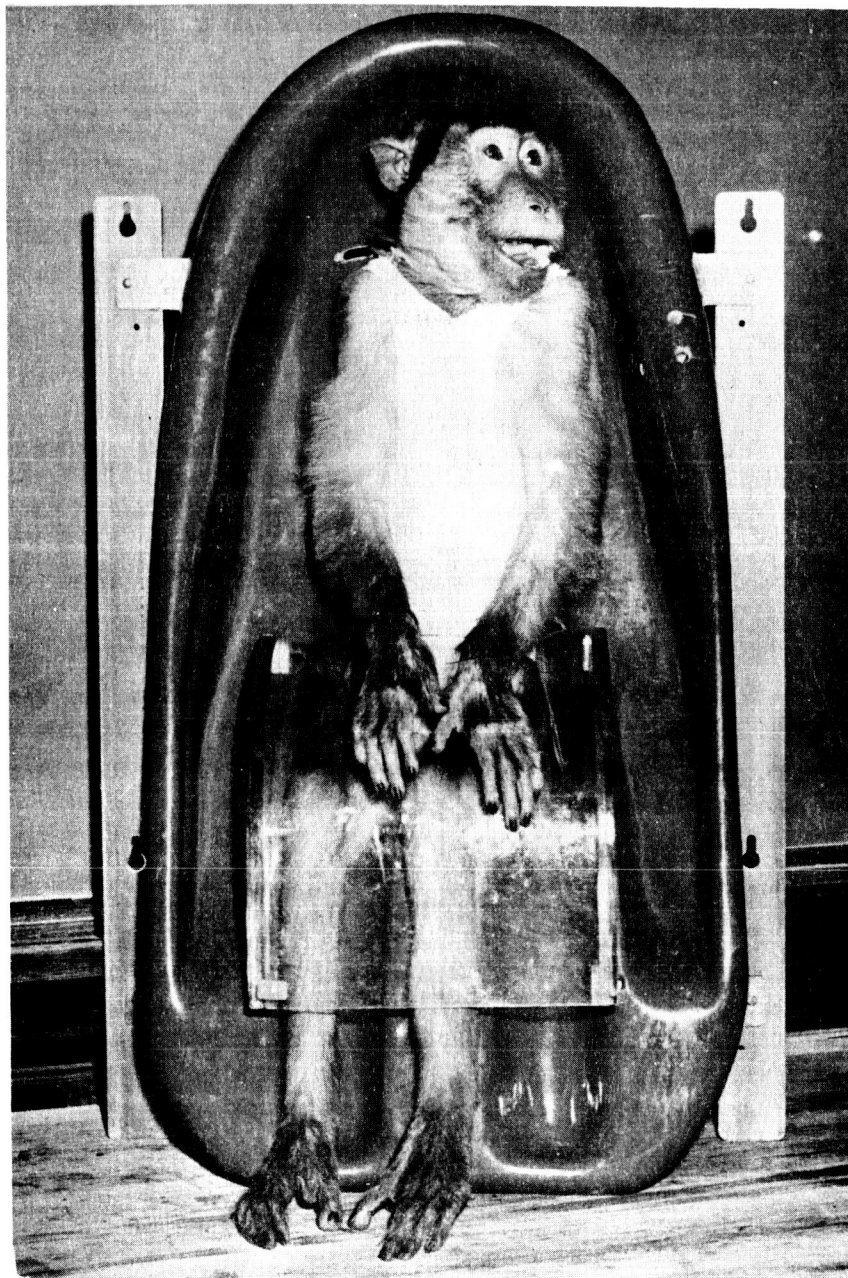


Figure 1.— *Macaca nemestrina* in the original Environmental Physiology Laboratory nylon-net restraint jacket and fiberglass couch.

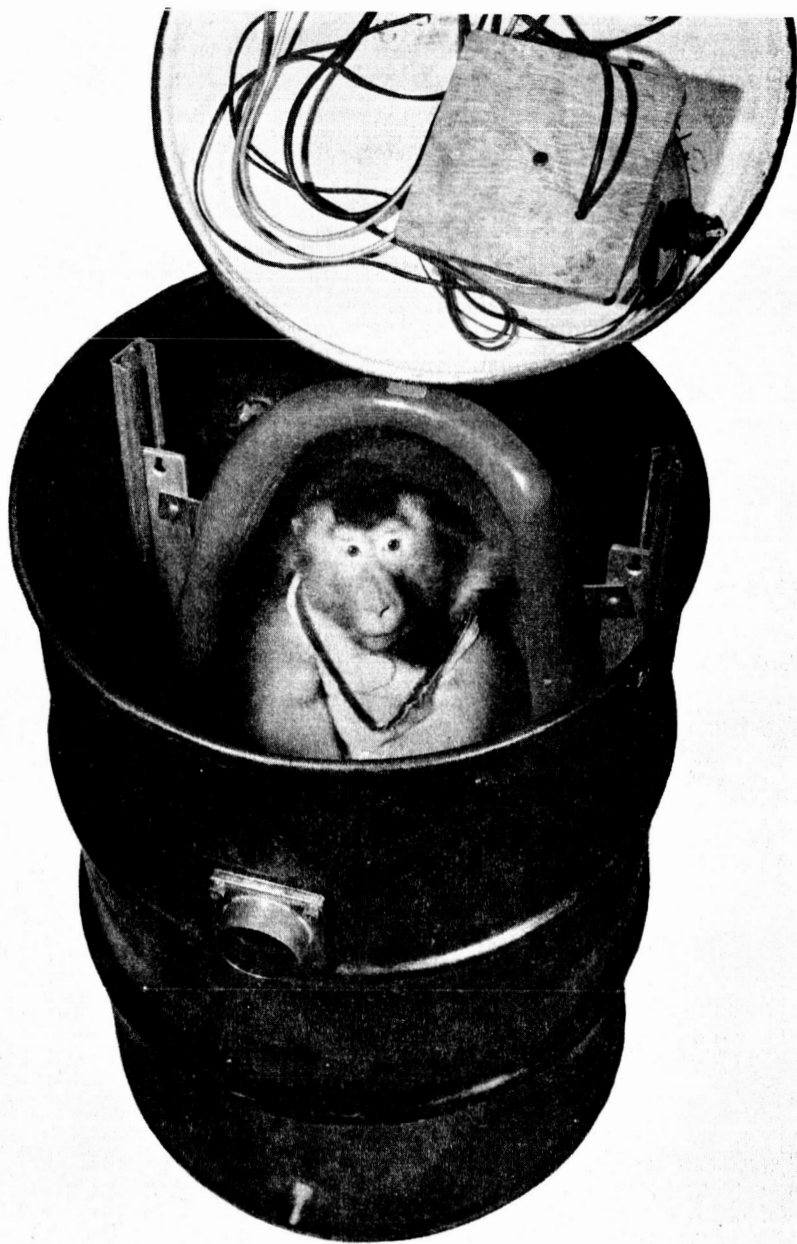


Figure 2.— Original apparatus used to measure respiratory gas exchange in *Macaca nemestrina*.



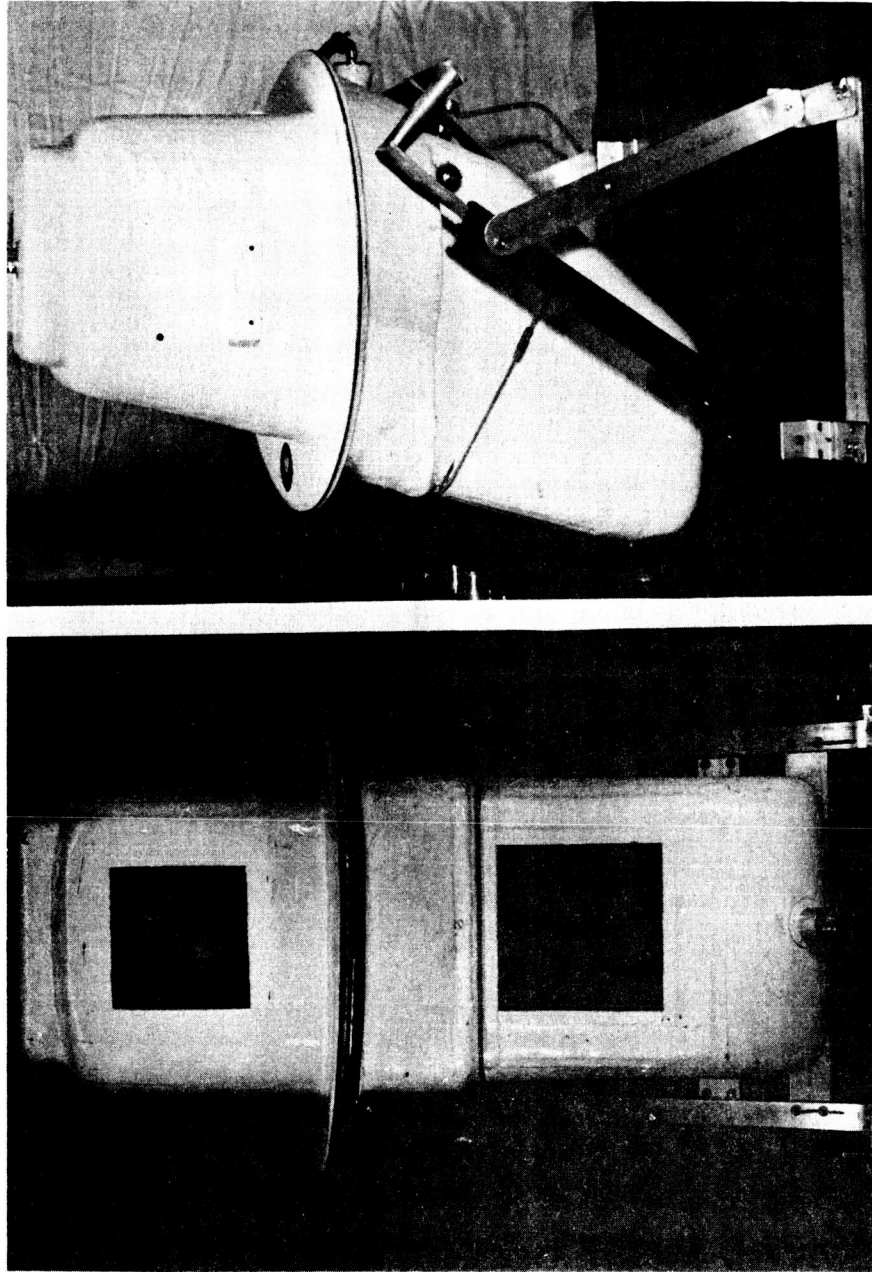


Figure 3.— Front and side views of the Environmental Physiology Laboratory fiberglass monkey pod.

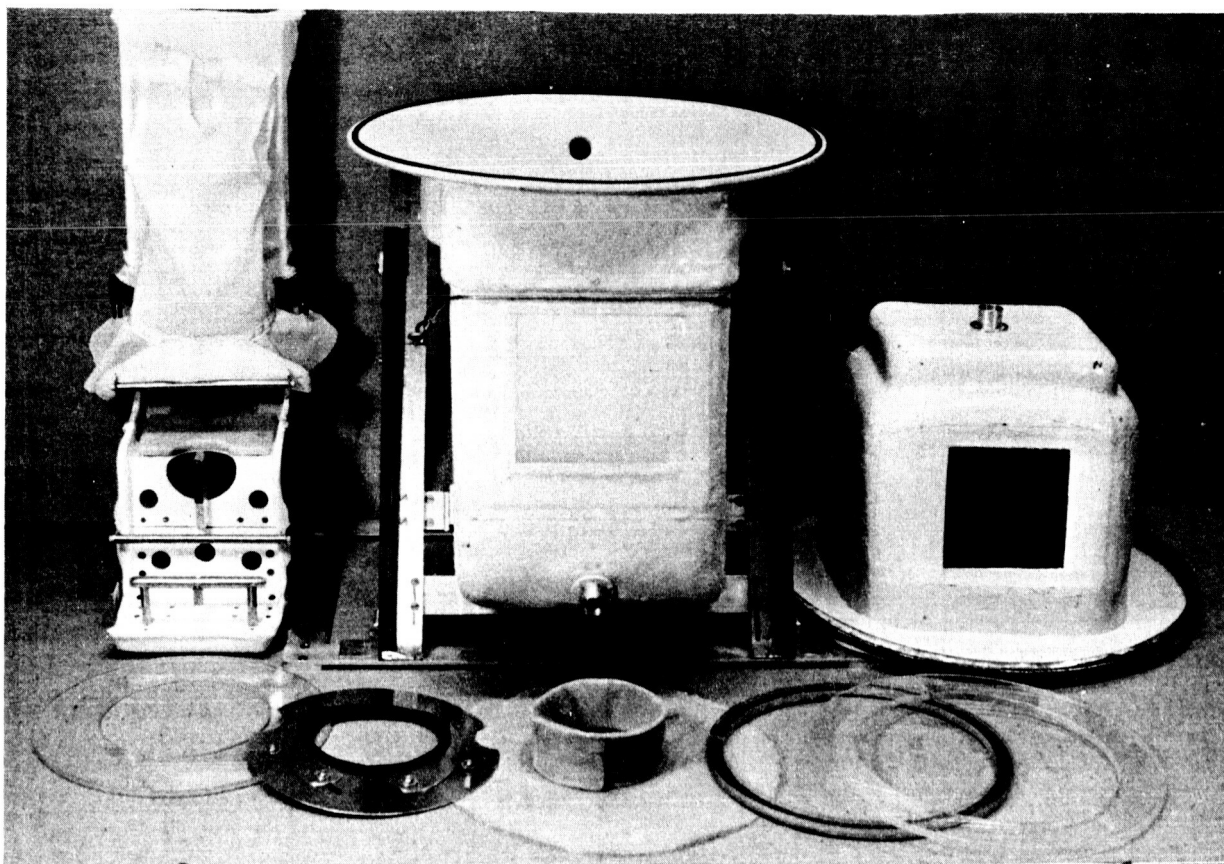


Figure 4.— Components of the monkey pod. At the upper left is the nylon-net restraint jacket and fiberglass couch combination which fits into the lower half of the fiberglass pod shown at top center. The upper half of the pod is at top right. The waist seal components are shown at the bottom, with the silicone-rubber belly-band and skirt at bottom center.

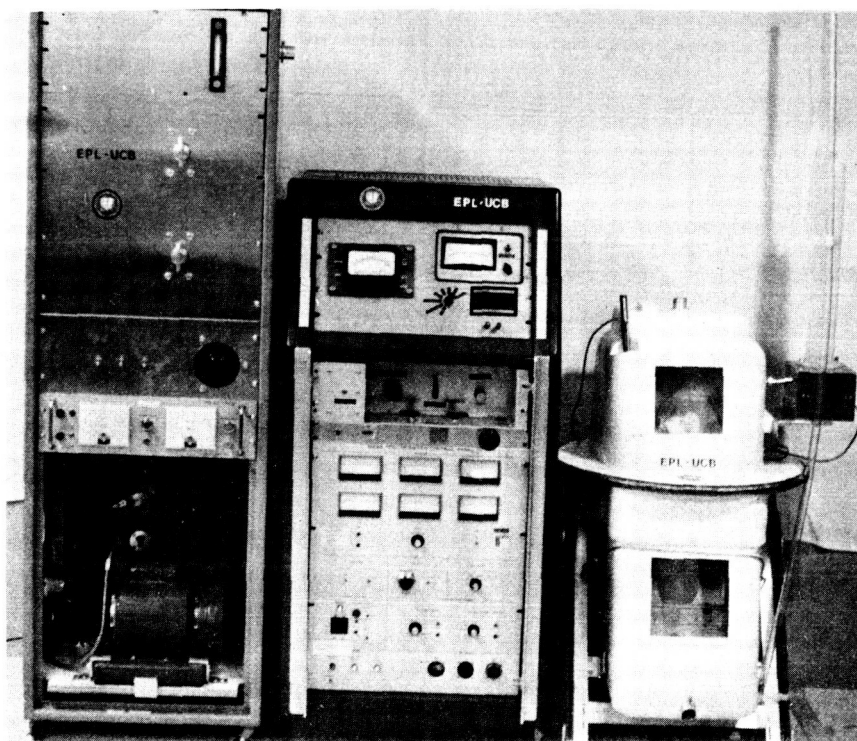


Figure 5.— The Environmental Physiology Laboratory monkey-pod experiment system used in two Shuttle Concept Verification Tests. The monkey pod and instrumentation console housing the mass spectrometer are at the right, and were located within the SPACELAB mockup. The console at the left housed vacuum pumps and a 28-V d.c. power supply, and was located outside the mockup.

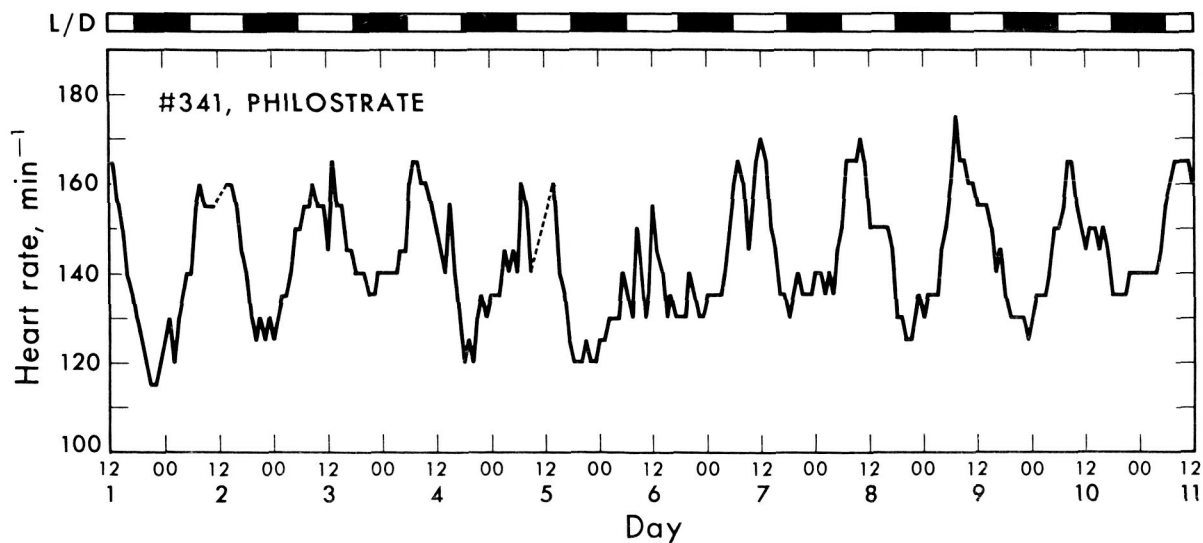


Figure 6.— Hourly mean heart rate of a 12-kg pig-tailed monkey during a 10-day pod experiment in February 1974. A 12:12-hr light-dark cycle was in effect, the light period being from 0600 to 1800 daily.

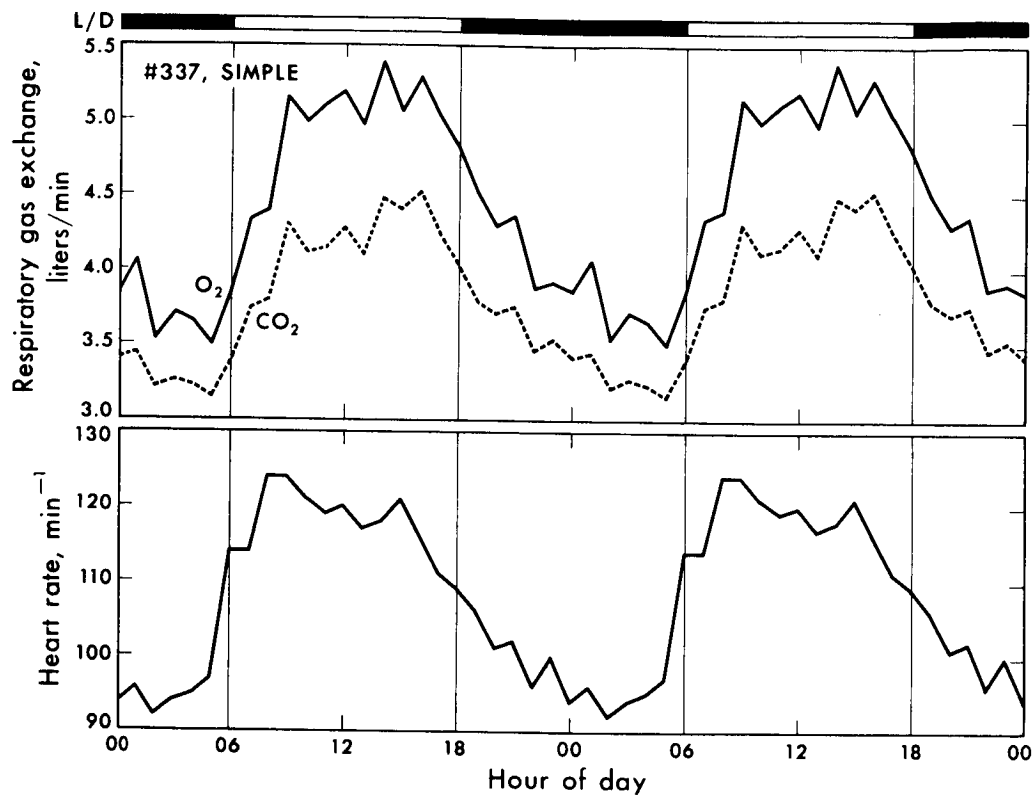


Figure 7.— Mean respiratory gas exchange and mean heart rate for each hour of the day during the 5-day NASA/MSFC CVT/GPL III in July 1974. Duplicate 24-hr cycles are shown.

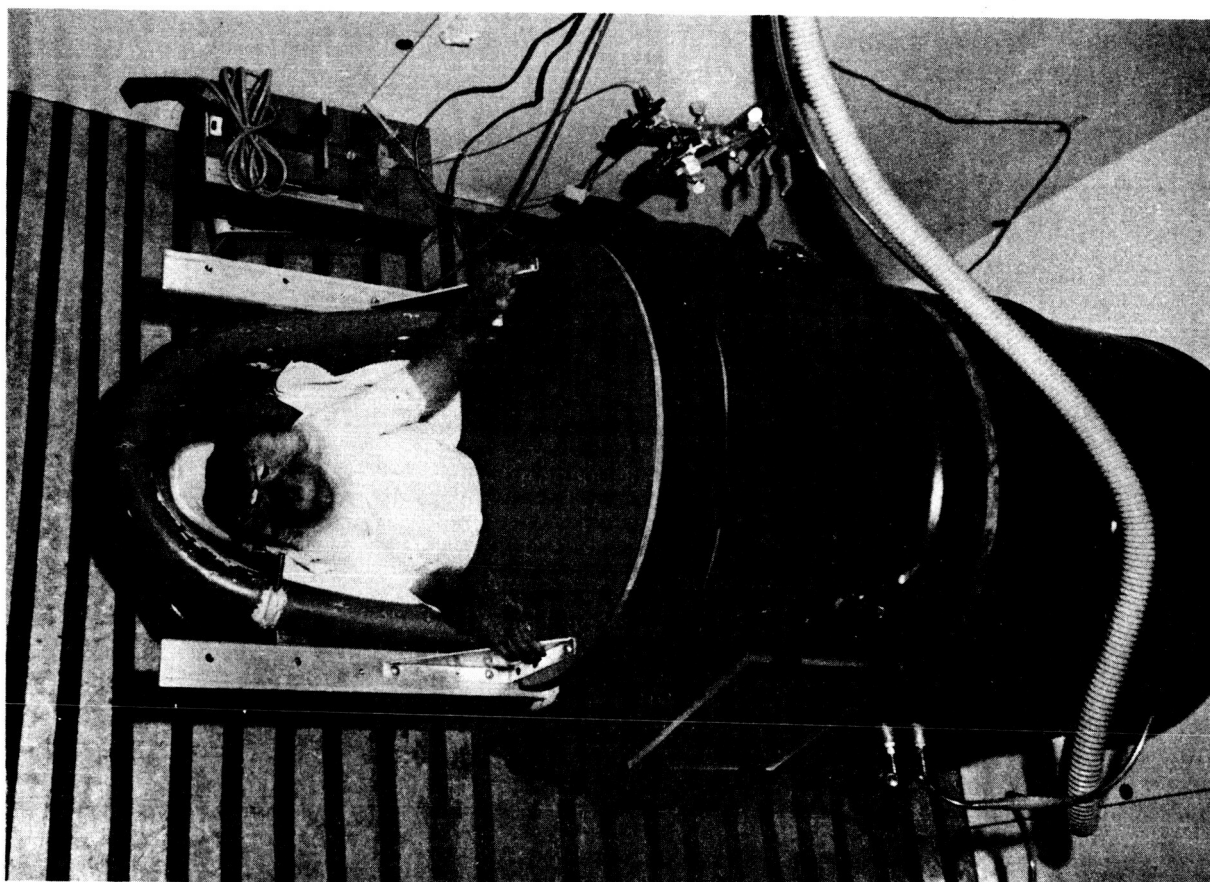


Figure 8.— Original apparatus used to measure cardiovascular responses to lower body negative pressure in the supine *Macaca nemestrina*.

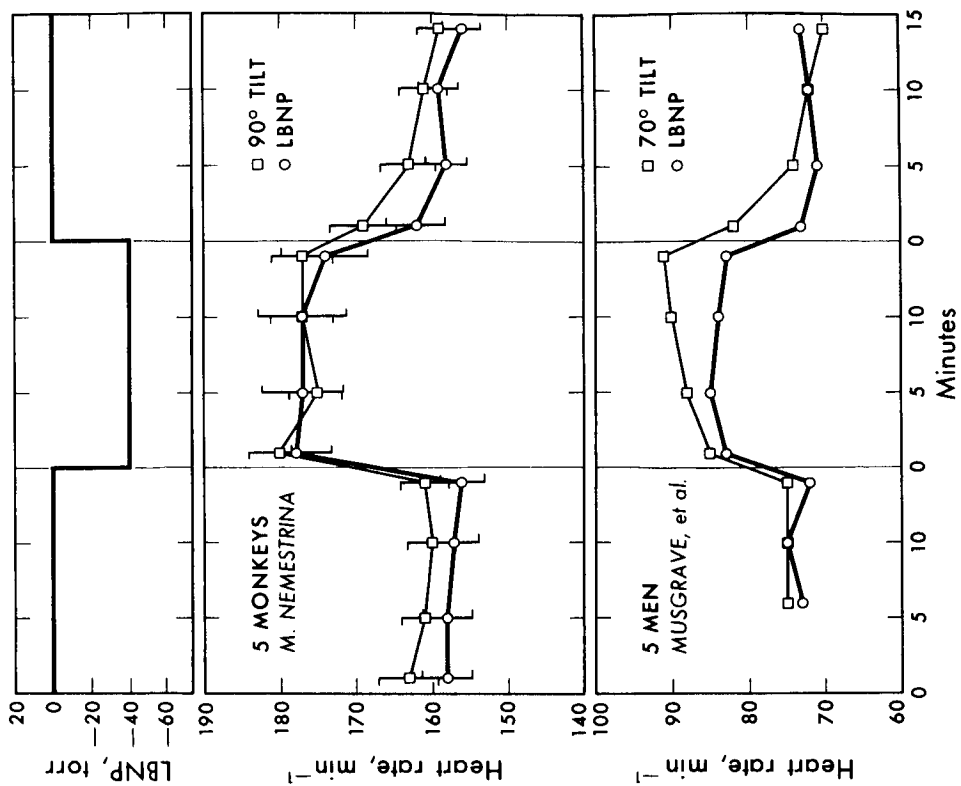


Figure 10.— Comparison of mean heart rate response to 40 torr of lower body negative pressure and vertical tilt from the supine position in five *Macaca nemestrina* and five men. Vertical bars about the mean show the standard error of the mean.

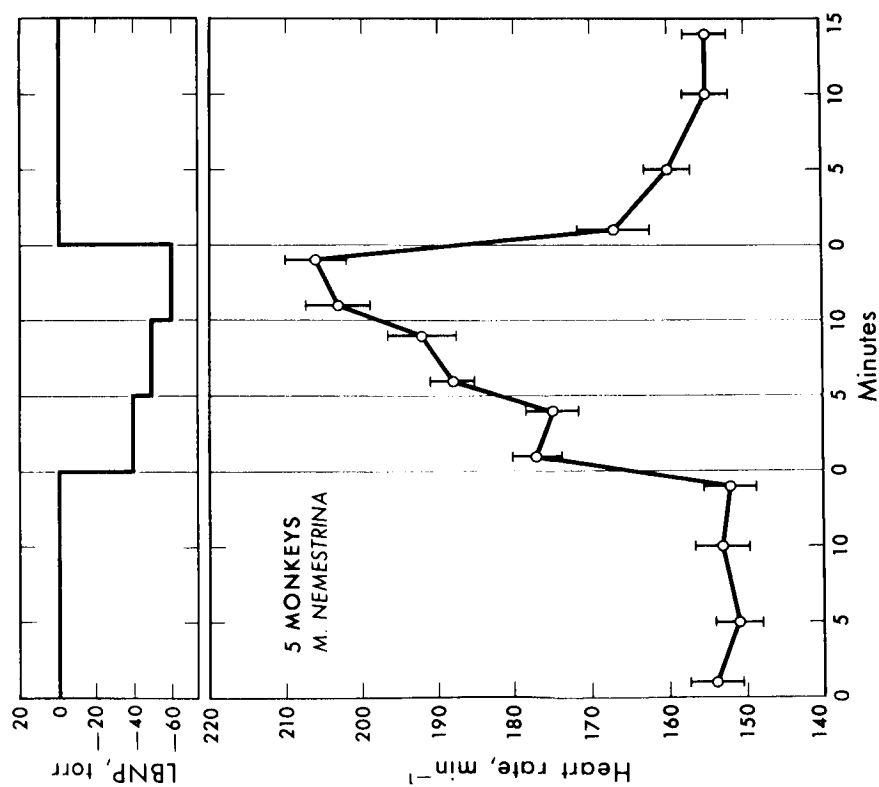


Figure 9.— Mean heart rate response to lower body negative pressure imposed on five *Macaca nemestrina* in the supine position. Vertical bars about the mean show the standard error of the mean.

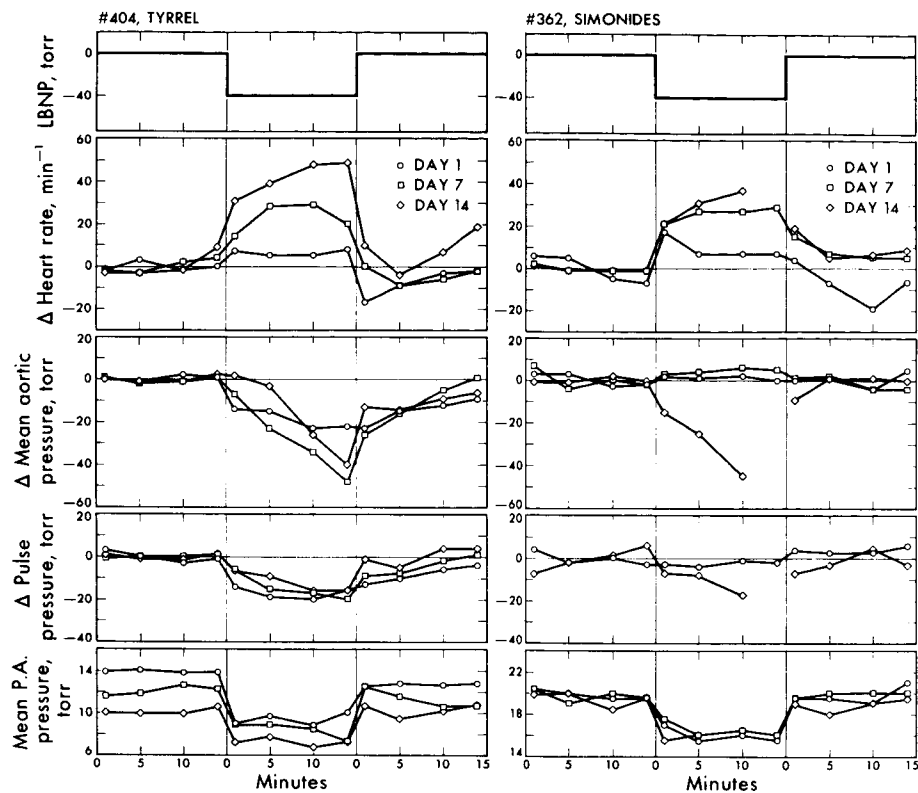


Figure 11.— Cardiovascular responses to 15 min of 40 torr of lower body negative pressure in two *Macaca nemestrina* during 14 days of continuous supine recumbency.

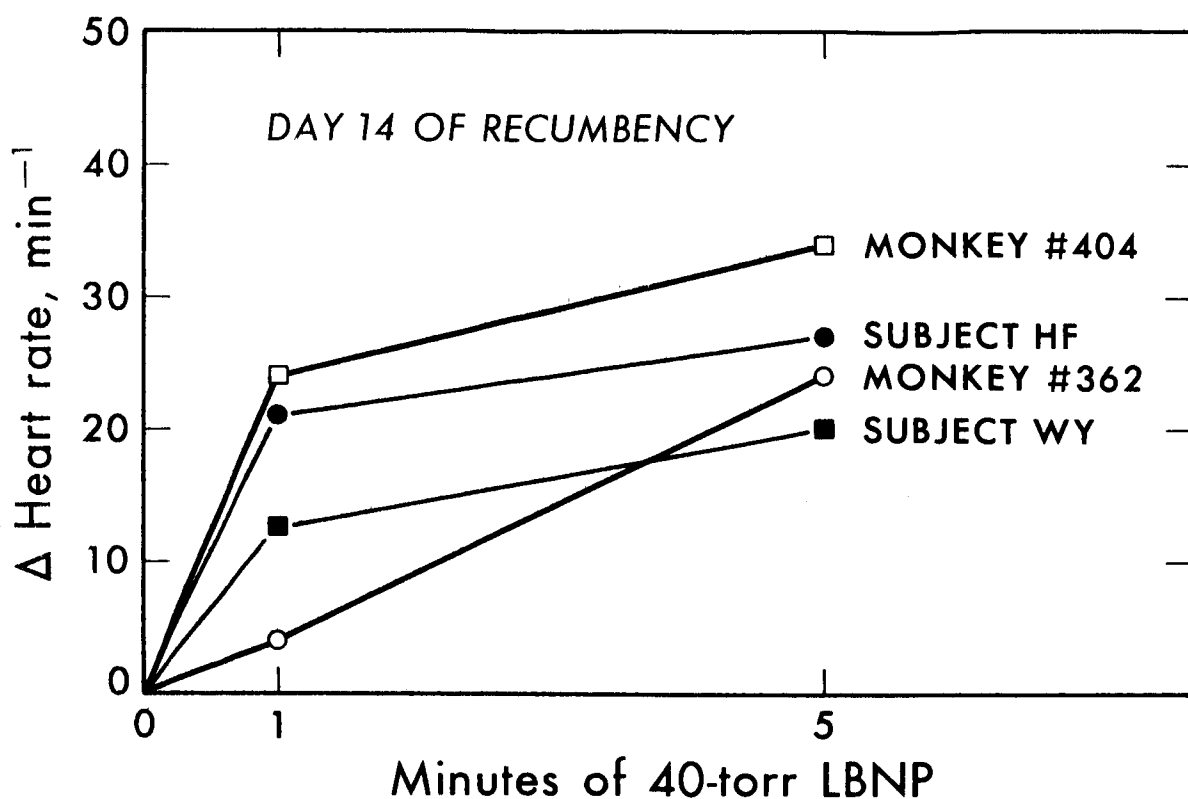


Figure 12.— Increase in heart rate response to lower body negative pressure on day 14 of continuous supine recumbency as compared to the heart rate response measured at the start of recumbency in two *Macaca nemestrina* and two men.



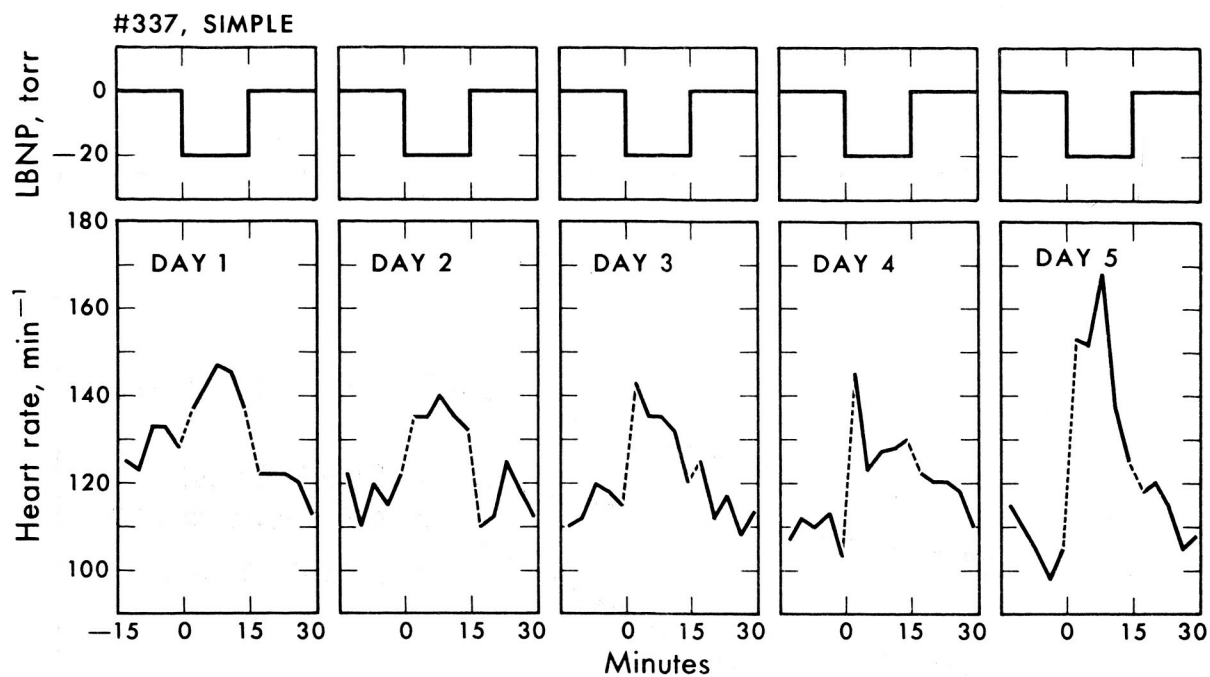


Figure 13.— Heart rate responses to 15 min of 20 torr of lower body negative pressure measured daily in the upright sitting position in the *Macaca nemestrina* subject of the monkey-pod experiment during the NASA/MSFC CVT/GPL III.

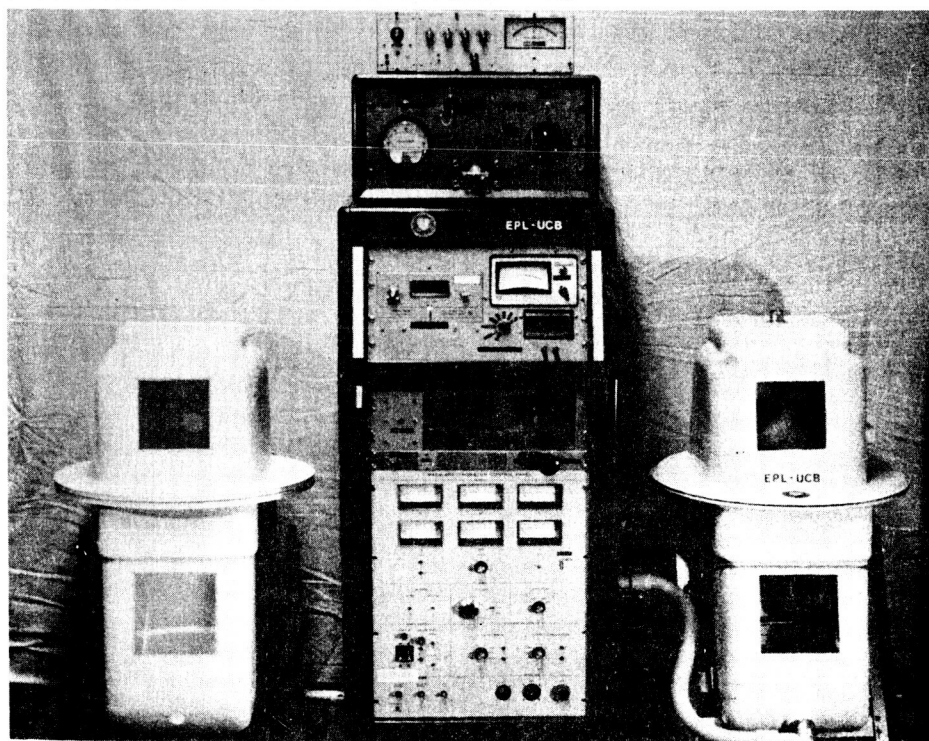


Figure 14.— Two-pod monkey experiment system utilizing common instrumentation on a commutated basis.

## THE ORBITING PRIMATE EXPERIMENT (OPE)

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### INTRODUCTION

Some cardiovascular, skeletal muscle, and bone changes have been seen in astronauts after space flight and have been recorded, not only for the various Mercury, Gemini, and Apollo Programs, but also for the Skylab Project. The Orbiting Primate Experiment, conceived in 1958 by Dr. Ashton Graybiel, Dr. Dietrich Beischer, and Dr. Harlow Ades of the Naval Aerospace Medical Research Institute in Pensacola, was designed to study the physiological effects of long-term weightlessness on the vestibular organs of an orbiting test animal and to investigate the microscopic changes which might occur in these organs.

Later, when G. Bourne and M. N. Golarz joined the project, the OPE posed the question, "Are there subtle changes so far undetected in an orbiting animal?" and suggested that some changes may occur in internal organs which do not produce clinical symptoms and cannot be detected in astronauts. Can, for example, pathological changes occur in the heart or other tissues without producing clinical or physiological symptoms, or without revealing themselves by changes in blood chemistry? If so, how extensive can they become before clinical or other symptoms appear?

Although it had been intended for the OPE to be part of the Apollo Applications Programs, now the Biomedical Experiment Scientific Satellite (BESS) would appear to be an appropriate vehicle.

The squirrel monkey had originally been chosen as the test animal because of its light weight and because weight was an important engineering factor at the start of the project. With the development of more powerful vehicles for space flight, the problem of the weight of the animal became less important, and in the late 1960's, a number of different monkey species were considered as alternatives. Other animals proposed were the pig-tailed macaque (*Macaca nemestrina*), the Java macaque (*Macaca fascicularis*), the red stump-tailed macaque (*Macaca speciosa*), and the rhesus monkey (*Macaca mulatta*). The rhesus monkey (fig. 1) was selected for a number of reasons: (1) there is an enormous amount of baseline information already available on the rhesus monkey, (2) it is a highly motivated animal, (3) it is hardy, (4) its behavior has been well studied, and (5) it is trainable, and its ability to perform has been well demonstrated.

Originally, veterinary support was provided by the Naval Aerospace Medical Laboratory headed by Dr. R. New and behavioral studies were under the supervision of Dr. Jack Thael.

Bourne and Golarz planned to study the histopathological and histochemical changes in skeletal muscles following exposure to extended periods of weightlessness. In 1967, they added to the project the study of the heart, other organs, and the skeleton. Hematology and blood chemistry were added later. The Naval Aerospace Medical Institute Veterinary and Pathology group, Dr. R. Brown, Dr. W. Britz, and Dr. J. Kupper, also carried out parallel hematological and blood chemistry studies, and they and their predecessors (Dr. R. New and Dr. Stephen Palmer) have been active

participants in all aspects of the project. Harold McClure and Michael Keeling, of the Yerkes Center, became active in the project in 1970. Dr. Harold Sandler, of the NASA Ames Research Center, has been a consultant on the cardiovascular aspects of this project since 1967, and more recently he has been joined by Dr. Lowell Stone of Galveston.

Officially known as the "Orbiting Experiment for Study of Extended Weightlessness," the project was described in some detail by Dr. Walton L. Jones in reference 1. It is the purpose of this paper to discuss various aspects of the program and to present the findings to date.

## EXPERIMENTAL PROFILE

The object of the OPE was to assess the changes induced by weightlessness in two or more unrestrained and minimally instrumented rhesus monkeys placed in a 200-n.mi. orbit above the Earth for a period of 6 months to 1 year. There were four basic requirements for the experiment: (1) weightlessness had to be isolated as a variable, (2) the experiment had to be long enough to cause some changes, (3) there should be no changes due to instrumentation, and (4) the techniques of observation should permit detection of subtle changes.

There were two aspects of the program which were subject to debate. Should the animal simply be required to press a button for food and to operate a lip action switch for water, no other demands being made on him for physical activity? Or should the animal be compelled to carry out calisthenic activity by moving levers many times to obtain his food? In other words, should the animal be forced or not to exercise while in the weightless state? In the former case, the effects of the exercise would probably be to reduce the changes which are due to weightlessness and might, in fact, cover up changes which would otherwise occur and which the experiment was designed to study.

It was intended originally that the OPE would be associated with the Apollo Application Program. The planned experimental profile was as follows: (1) two animals would be flown, (2) the monkey space capsule, which would be self-sustaining, would fit onto the rack in the Apollo service module on which the lunar lander was stored in the Apollo mission, (3) the monkey capsule would be established in a 200-mile orbit, (4) the capsule would orbit 6 months to 1 year, (5) the Apollo command module would rendezvous and dock with the monkey capsule, (6) one of the astronauts would carry out EVA to activate the mechanisms in each monkey cage to force the monkey into a carrying box, (7) each carrying box would be detached from the monkey capsule and conveyed to the command module and stored, (8) the command module would return to Earth, and (9) the animals would be sacrificed and subjected to detailed autopsy, or one would be kept alive for a time for a parallel physiological study and sacrificed later. This profile is shown briefly in the launch operation sequence demonstrated in figures 2 and 3. The sequence of events is taken from the Northrop Company's report to Langley Research Center, NASA document CR 66511 (NSL 67-300).

Following is the sequence of major events that make up the launch booster phase:

1. Saturn S-IB ignition and liftoff
2. Saturn S-IB burnout and separation

3. Launch escape system (LES) jettison
4. S-IVB ignition
5. S-IVB burnout at 100 n.mi. Earth parking orbit altitude.

After the S-IVB stage places itself, the CSM, and the Primate Spacecraft onto the parking orbit, the CSM separates itself and the spacecraft and performs an orbital altitude change. This maneuver consists of: (1) one CSM main engine thrusting period to change orbital velocity from a value that would just sustain a 100-n.mi. altitude to one that would result in a 250-n.mi. apogee altitude; (2) a coast period from 100 to 250 n.mi. altitude (one-half orbital revolution); (3) and a second CSM burn that would increase apogee altitude velocity to a value that would result in a 250-n.mi. circular altitude. After a short checkout, the CSM crew would then release the spacecraft.

The sequence of events for the Primate Spacecraft is as follows:

1. Apollo crew determines from onboard and ground tracking data that the proper Earth orbit has been achieved.
2. CSM releases from SLA, rotates and docks with LEM ascent stage or LEM substitute.
3. CSM, LEM, or LEM substitute and spacecraft separate from S-IVB.
4. Astronauts perform status check on spacecraft.
5. CSM performs Hohmann transfer maneuver from 100 to 250 n.mi. altitude.
6. CSM releases spacecraft to orbit on its own for upwards of 1 year.

At the time of final spacecraft separation from the CSM, the experiment must be capable of operation independent of the launch vehicle that placed it in orbit.

1. The orbital phase of the mission starts at the point where the Primate Spacecraft is physically released from the CSM and continues to the point in the mission (approximately 1 year later) where an astronaut from a second Apollo vehicle retrieves the primates. Spacecraft sun orientation and communication establishment with ground stations constitute the major events.

2. The recovery and reentry phase of the mission actually starts with count-down of the Apollo launch vehicle that will return the primates to Earth. For purposes of establishing requirements and constraints that affect the spacecraft design, however, the mission profile is assumed to start in this phase with the docking and EVA required to bring the live primates on board the Apollo CM. The primates, enclosed in individually sealed recovery capsules, will then be stored aboard the CM, after which a standard Apollo reentry maneuver will be conducted. The recovery and reentry phase is complete at the time of CM touchdown in the WTR recovery area.

Following is the sequence of events for this phase of the mission, assuming that the CSM has arrived in a position to start the docking maneuver:

1. The CSM docks with the Primate Spacecraft after a spacecraft status check is received and evaluated.

2. The Astronauts activate EVA aids (handrails, etc.) and suit up in preparation for decompression of the CM interior.

3. A single astronaut performs EVA and arrives at the recovery capsule locations at the outer skin of the Primate Spacecraft.

4. Astronaut activates the manual capsule releases, removes the capsules from the spacecraft, and returns to the hatch of the CM.

5. The second astronaut brings the capsules inside of the CM and stores them in the CM storage areas.

6. The CM hatch is then closed, the CM repressurized and a standard reentry procedure is started.

7. The Primate Spacecraft is jettisoned.

8. Retro-maneuver is completed and the SM is jettisoned.

9. Aerodynamic reentry is conducted.

10. Drogue and main chutes are deployed.

11. Splashdown in CM recovery area is conducted.

Recovery of the primate capsules (canisters) by EVA is shown in figure 4.

### Capsule Design

Two life support systems were designed for the OPE, one by the Northrop Company and the other by the Lockheed Company. The main differences between these two designs were in the shape of the animal area, the method of transferring the animals into the transport cage, and the method of administering the food pellets.

A model of the Northrop version of the spacecraft is shown in figure 5. The shape of the animal area, which contains a toy monkey (disproportionately large), can be seen in the cutaway section. The "floor" is an arc of a circle, and the vertical wall can be actuated to sweep up to the "roof," forcing the monkey before it until the animal moves finally into the transport box seen projecting from the roof of the capsule on the right. The Primate Spacecraft configuration is shown in figure 6 and the Primate/Life Cell Interface in figure 7. The Northrop recovery mechanism is demonstrated in figure 8.

It was estimated that approximately 30,000 pellets (each weighing 0.623 g coated and 0.607 g uncoated) would be needed to sustain a 12 to 15-lb rhesus monkey for 1 year. The Northrop method of administration consisted of aligning these pellets into approximately one-half mile of zippered plastic tubing and winding this tube onto a reel. The lip-action switch pressed by the animal would

advance the tube one pellet, it would be split open by the mechanism as it advanced, and the pellet would be propelled into the animal's mouth.

The Lockheed animal compartment was a cylinder with the central portion of the floor movable. When it was necessary to catch the monkey, walls of the compartment would fold towards the center and the movable portion of the floor would move up like a piston, pushing the animal into a small canister on the top of the spacecraft. That part of the floor would then lock onto the bottom of the canister providing an air-tight seal (fig. 9).

Both the Northrop and Lockheed transport canisters were to contain an independent life support system which would maintain an animal for 24 hr.

In the Lockheed feeding system, the food pellets were kept in a spring-loaded hopper, and individual pellets were released by the lip-action switch.

It was planned also to carry out mass measurement studies of the animals periodically during the flight. This was to be accomplished by a mechanism involving air displacement. At the sound of a buzzer the animal was trained to enter a small compartment, the door of which would then close. The air displacement would be measured and telemetered to the ground; the weight of the animal could then be calculated.

At this stage, although a good deal of attention had been paid to the accommodations for the monkeys, there was still a need to know more about the reactions of the animals themselves in such an environment. They learned quickly to operate lip switches and more complicated equipment designed to exercise the animal, but which had not at that time been included in the schedule. To test their adaptability to zero G, rhesus monkeys were flown by regular aircraft in a series of Keplerian trajectories. They showed some fear at the beginning, but adapted to the strange situation, giving evidence eventually of enjoying the sensation of weightlessness (fig. 10).

A technical feasibility demonstration model of the life support system of the capsule was constructed and was tested at the Naval Aerospace Medical Research Institute in Pensacola. One half was constructed by the Northrop Company and one half by Lockheed. They were placed alongside each other, a monkey situated in each, and were operated for varying periods of time, the longest period being 4 months. Although there were problems with some of the lip-action water switches and other minor problems, the life support model functioned well (fig. 11).

### Preflight and Postflight Studies

The objectives of the experiment were to make as many measurements of the animals as possible before and after flight. With the minimal instrumentation proposed, in-flight measurements were limited and were to be restricted to periodic mass measurements, temperature telemetry, ECG telemetry, and television observation.

Immediately prior to the flight it was planned that the following tests be carried out on flight candidate monkeys and their controls: blood chemistry, hematology, viology, bacteriology, body weight, anthropological measurements, tests for vestibular function, ECG, ophthalmology, and general clinical observations. Muscle biopsies were also to be taken long enough before flight time

that the wounds would be completely healed. The possibility of performing needle biopsies on other organs, e.g., liver and kidney, was considered, but was not accepted.

The hematology studies planned included hematocrit, hemoglobin, red blood cell count, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration (MCHC), reticulocyte count, platelet count, white cell count, and differential white cell count.

The blood chemistry studies included cholesterol, uric acid, total protein, albumin, globulin, alkaline phosphatase, creatine phosphokinase, lactic dehydrogenase (LDH), electrolytes, calcium, phosphorus, sodium, potassium, chloride, carbon dioxide, blood glucose, serum lipase, serum amylase, BUN, and creatinine.

Microbiological studies on the animals would include an investigation of nasal cultures, pharyngeal cultures, rectal cultures before and after flight, and other studies would include antibiograms, animal pathogenicity studies, and lyophilization studies. Virology studies included serology, stool and throat sample cultures.

Immunology studies were to be made also. Serum samples would be obtained 1 week prior to launch. This would be the preflight antibody control sample. Another sample would be obtained as soon as possible after return to Earth. At the same time, the animal would be injected with keyhole limpet hemocyanin, sheep erythrocytes, and dinitrochlorobenzene. Further serum samples drawn 7, 14, and 21 days after flight would be tested for antibodies. Similar tests would be carried out on the ground controls.

Urinalysis would be performed preflight and postflight. No in-flight studies would have been feasible in the original OPE, but the collection of urine samples may be possible in the future if the animals are flown in the Space Shuttle under human supervision or even in BESS. The studies to be made on the urine would include color, turbidity, specific gravity, glucose, ketones, pH, bilirubin, creatinine, sodium, and potassium.

Studies of various organs would be made postflight following autopsy. The results would be compared not only with those obtained from the ground controls for the flight, but with a large series of controls accumulated over the preceding years. For example, the heart would, of course, be studied by preflight and postflight ECG's and in-flight ECG's by telemetry. The gross weight of the heart would be obtained at autopsy; it would then be sectioned and a detailed study of the histopathology, histochemistry, and electron microscopy sections carried out. Histochemical studies for heart sections and those of all other tissues would include polysaccharides, calcium, fats and lipids, and 10 enzymes. Bone would be studied (1) by preflight and postflight radiography of chest, abdomen, head, arms, and legs, (2) by measuring the amount of bone salt in various parts of the skeleton, (3) by histological study of bone sections, and (4) by study of gross sections of heads of long bones, vertebrae, and fingers to observe changes in the pattern of trabeculae. Skeletal muscle would be studied by electromyography, histopathology, histochemistry, and electron microscopy. Other organs would be subjected to the latter three procedures.

## Nutrition and Feeding of Flight Animals

The monkeys were to be fed by means of a dispenser which, upon actuation, would provide a small pellet of food. The Purina Company developed a small pellet, based on Purina Monkey Chow, which was intended to include all the factors necessary for adequate nutrition for periods of 6 months to a year. These pellets were fortified with vitamins A and C, and some of them were given an additional coating to retard the oxidation of the vitamins. The uncoated tablets weighed 0.607 g and the coated tablets weighed 0.623 g. The only fluid available to the animals would be distilled water.

Young monkeys tested for a year on these pellets as their only source of food, together with distilled water, survived very well and continued normal growth. Hematological and blood chemistry values remained within normal limits for the duration of the experiment, and histological, histochemical, and electron microscope studies of the animals organs and tissues showed them to be normal. The animals consumed, on an average, 300 tablets (about 250 g) and approximately 1000 cm<sup>3</sup> of water a day. (The animals would require twice this amount of water for waste management in the airstream.)

A series of monkeys were also trained, at the Aerospace Medical Research Institute at Pensacola, to carry out calisthenic activities to obtain food. Studies were made on the calibration and perfection of equipment for Earth control of calisthenic behavior so that the number of times the animal had to press levers to obtain food could be controlled from the ground. Other ground experiments included three test runs of the technical feasibility demonstration model of the flight life support hardware, perfection and testing of food and water dispensers, the design and testing of the monkey mass-measurement device, and the development and testing of the temperature telemeter and ECG devices. Preliminary studies on simulated solar flare exposure, using the NASA cyclotron in Williamsburg in association with Dr. Hank Aceto, were also carried out.

## Waste Management

Waste management in a weightless environment represents a special problem, especially for unrestrained animals, and is of a double nature. (1) The waste material (urine and feces) and unused food have to be removed from the animals' environment. (2) The waste material has to be disposed of.

For the technical feasibility demonstration model (TFDM), the Lockheed Company designed a waste management system which dealt with the second of these problems. They used a sheet of thick fiberglass wool, which was folded in an accordion fashion and impregnated with phosphoric acid, which deodorized and sterilized the excrements falling onto it. This form of waste management was used in the TFDM and in a 4-month run proved very successful. Subsequently, the Lockheed Company found that it effectively handled the waste material of a rhesus monkey in a year-long test. However, in the weightless state the feces and urine will not drop down onto an absorptive material and will have to be forced there by laminar air flow. A continuous flow of 1 ft/sec had been projected for the OPE, but a higher rate of flow may be required in practice.

There was no information as to the effects of such an air flow on rhesus macaques over a long period of time (e.g., 6 months). It is possible that the animals could become dehydrated or



susceptible to infections. The effect of air flow on rhesus monkeys is now being tested at the Yerkes Center. Two air flow chambers have been designed by Prof. H. Warner and Ed Bridges of the Yerkes Center in which an effective laminar flow has been produced. The laminar nature of this flow is very well shown in figure 12, which shows a line of smoke extending from the top of the cage to the bottom. Figure 13 shows a series of such lines. Two monkeys have been kept in these chambers for a 6-month period at a flow rate of 1 ft/sec. The animals have survived, and their blood chemistry and hematology appear normal. Further tests are now taking place in which the flow has been doubled to approximately 2 ft/sec.

### Flight Animals

Originally it was planned to use the standard wild-born rhesus macaques as purchased from animal importers, but when studies were made of the skeletal muscles of these animals, it became apparent that all wild-born animals showed a number of foci of myopathy. Such animals, of course, would be useless for studying muscle changes in weightlessness. It became obvious, therefore, that because of the limited number of captive-bred animals available in the United States, a breeding colony of rhesus macaques would have to be established under controlled conditions. An initial breeding compound was constructed at the Yerkes Field Station to produce animals whose medical history would be precisely known. A second breeding compound has now been added.

Monkeys to be used in space should be behaviorally, as well as physically, normal. After discussion with a number of behaviorists, it was agreed that the formula for obtaining behaviorally normal young animals would be (1) that the infants must be brought up with their mothers for at least the first year of life and (2) that they be given an opportunity during this time to associate with their peers. These conditions, it was agreed, could be met by compound breeding, but not by cage breeding. The following procedure was therefore adopted and is currently being used. The young animals are left with their mothers for a year; this enables them to obtain the mother love, care, and protection they need and gives them a feeling of security, but at the same time it enables them to interact with other young animals in the compound. After a year the young males are harvested. They are then kept for another year in large, modified cages constructed from commercial corn cribs, in a gang-cage-type of group living. During this time, clinical, neurological, ophthalmological, behavioral, microbiological, hematological, and blood chemistry studies are made. Animals which are normal in all these parameters are then moved as flight candidates to a conditioning facility located at the main Yerkes Center. These animals are isolated in pairs in a fiberglass-lined mobile unit with strict hygienic control and with limited access by humans. Special attention is paid to their diet to be sure that nothing is lacking nutritionally, and they receive periodic physical and behavioral evaluations. There are also periodic clinical laboratory studies which include not only hematology and blood chemistry, but microbiology and virology as well.

The Yerkes Field Station can be seen in figure 14. At the bottom of the left of the group of structures in the center of the photo, two adjoining large compounds, with the lower one subdivided into two smaller compounds, can be seen; these are the two main compounds which are used for breeding monkeys. They are each 125 ft<sup>2</sup> with walls 14 ft high with 6 ft of chain-link fencing on the ground and surmounted by 8 ft of sheet metal. This effectively confines the animals. The floor of the compound is covered with gravel and some grass, and the animals are provided with climbing structures and also with cement culverts in which they seek cover in inclement weather. The den or sleeping quarters consists of a mobile trailer 40 ft long with a cross section 8 ft high by

10 ft wide. There are two swinging doors, one at each end, which open into the compound. The presence of the two doors protects an animal from being cornered and attacked inside the sleeping quarters by another monkey. Perches for the animals are in the form of horizontal parallel bars running along the whole length of the inside of the trailer. The trailer is heated in winter and cooled in summer.

Figure 15 illustrates the walls of the outside enclosure with the chain-link fencing and sheet metal above it, the culverts with animals sitting in them, and also the climbing structures. The sleeping quarters, or den, which are attached to the side of the compound, can be seen in figure 16. Situated near the compounds are modified corn cribs (fig. 17) which are mounted on concrete slabs. To the left is a small den which is heated in cold weather and used by the animals for sleeping. Figure 18 is a closer view of the corn cribs with the animals in them.

At the main Yerkes Center, the conditioning facility for flight candidates is 50 ft long, 10 ft wide, and 8 ft high, containing tall cages with the approximate capacity which had been planned for the animals in space (fig. 19). Figure 20 shows the interior of the trailer with the cages in which pairs of animals are confined.

The birth data from the breeding program are shown in table 1. The data indicate an 11.59 percent mortality over a 5-year period, while published figures show a 15 percent mortality for caged rhesus macaques (ref. 2).

## CURRENT GROUND STUDIES AND RESULTS

In addition to studies directly concerned with space flight, some ground studies have been carried out at the Yerkes Center using enforced bedrest on rhesus monkeys. Loose, whole-body casts which extend from the ankles to the armpits were applied on the animals, the arms and hands of the animals left free. They were placed on a modified primate-restraint chair which kept them in a horizontal position, and they were turned from supine to prone position several times daily to avoid pressure sores and respiratory congestion. To avoid the stress involved in such restraint the animals were housed in a laboratory which they shared with four technicians who gave them constant attention and grooming. Furthermore, two animals were used at one time and were placed close to each other so that they could carry out mutual grooming. Preliminary studies by Dr. Joan Danellis and her colleagues at the Ames Research Center demonstrated in one animal that the stress hormones fell to near normal levels within a week to 10 days of the animal being placed in restraint. After 6 months in this state of restraint the animals were sacrificed, and detailed histology, histochemistry, and electron microscopy were done on all the organs. For 1 month prior to restraint and during the restraint period itself, weekly blood samples were taken for blood chemistry and hematology.

Figure 21 shows one of the restrained monkeys receiving attention from one of the technicians. Figure 22 shows two rhesus monkeys in restraint lying next to each other and engaged in mutual grooming, an activity which occupies their attention for hours. The animals appeared to adapt very well to this type of restraint, seemed to enjoy the human company which went with it, and certainly very quickly integrated themselves into the life of the laboratory and behaved as if they were part of it. We feel that the integration by the animals into the laboratory life is an

important part of this experiment because it reduces the stress which the restraint imposes on the animals, and this stress could be an additional variable in the experiment. In studies underway at this time, animals that initially react too strongly to the restraint of the whole-body cast are discontinued immediately from the experiment.

So far six animals have been subjected to a period of 6 months each in the restraint described, the results of which showed: (1) there was no significant change in organ weight; (2) fat accumulated in kidney tubules, heart, liver, and in the intima of the aorta; (3) there was an increase in fibrous tissue in the heart and a decrease in size of heart muscle fibers (fig. 23); (4) in one animal there was a dilatation of spaces between cardiac fibers and accumulation of fluid and vacuolar degeneration (fig. 24); (5) liver cells were degenerating in one animal, with the accumulation of fluid and cell debris between the cell cords (fig. 25); (6) there were possible fatty changes in some parathyroids; and (7) there was atrophy of type I fibers in the skeletal muscles (fig. 26). Blood studies on these animals showed no consistent changes in the red blood cell count or in the appearance of red blood cells. The white blood cells showed a consistent increase. This increase of white blood cells in most animals was due to an increase in segmental cells. There was a consistent decrease of the mean corpuscular volume and a consistent decrease in the mean corpuscular hemoglobin. There were erratic changes in the uric acid, and there was a large increase of alkaline phosphatase in two animals. The creatine phosphokinase showed a large increase in the same animal that showed severe heart damage. The SGPT and SGOT levels showed a drop in two animals. There were negligible changes in the sodium and potassium levels.

Dr. Harlow Ades, Bioacoustics Research Laboratory, Department of Electrical Engineering, University of Illinois, continues his studies of fine structure of the vestibular organ of the normal rhesus macaque using both transmission and scanning electron microscopy. These studies are being carried out at the University in Urbana and in association with Dr. H. Engstrom, Ear, Nose, and Throat Department, University of Uppsala, Uppsala, Sweden.

## PRESENTATION TO SPACE MEDICINE REVIEW COMMITTEE

In 1971 the OPE program was presented to the National Academy of Sciences Space Medicine Review Committee. The aspects presented were: (1) rationale, (2) effects of long-term weightlessness on vestibular organs, (3) scaling experiments from rhesus monkeys to man, (4) vestibular organ structure, (5) vestibular clinical tests in rhesus monkeys, (6) life support hardware for the OPE, (7) medical protocol for the OPE experiment, (8) the integrated medical and behavioral laboratory measurement system, (9) the integrated medical and behavioral laboratory measurement system in the OPE, (10) the incorporation of the integrated medical and behavioral laboratory measurement system and OPE into a Skylab configuration, (11) mass measurements of OPE monkeys in the weightless state, (12) physiological correlates of acute food and water deprivation in *Macaca mulatta*, (13) food tablet development for the OPE, (14) calisthenic behavior in the rhesus monkey as a countermeasure to weightlessness, (15) behavioral protocol, (16) results of behavioral protocol levels, (17) bacterial implications of the OPE, (18) viral implications of the OPE, (19) implantation of biotelemeters into OPE monkeys, (20) experiment hardware results, (21) baseline studies at the Yerkes Primate Research Center, and (22) summaries and issues.

Following the presentation, the Space Medicine Committee commended the scientific way in which the project had been approached and recommended that it be continued.

## SUMMARY OF THE ORBITING PRIMATE EXPERIMENT

### Object

The object of the OPE is to fly unrestrained, minimally instrumented, rhesus macaques in orbit for periods up to 6 months or 1 year.

On return from orbit the following studies would be carried out:

1. Tests for vestibular, cardiovascular and skeletal muscle function.
2. Detailed blood chemistry and hematology.
3. Tests for immunological competence on selected animals.
4. Bacterial and viral studies based on nasal, rectal, and throat swabs.
5. Histopathological and histochemical study of all organs and tissues, including the vestibular organ, using light and electron microscopy.

### Rationale

Studies on astronauts and individuals during prolonged bedrest have indicated that the three most important changes which occur in the human body and which are reversible on return to a normal environment are loss of bone salt, cardiovascular deconditioning, and loss of skeletal muscle substance. The question that has to be answered is "Do any anatomical, pathological changes occur during long periods of weightlessness (6 months or longer) which may not be reversible or which might hinder the resistance of the individual to the additional G forces that would be met on return to a normal environment?" Supplementary questions would be "How early do these changes, if any, commence and how early in the weightless environment could they be detected? Would all such changes be reversible on return to a 1-G environment?"

### Instrumentation

Because instrumentation is itself likely to induce tissue changes which can be confused with those produced by extended weightlessness, it was planned to reduce the amount of instrumentation in the flight animals to a minimum. In the original OPE, an ECG telemeter and a temperature telemeter were planned. In association with Dr. Harold Sandler and Dr. Lowell Stone, the additional possibility of the insertion of a pressure sensor in the ventricle of the heart is now also being considered.

## Nutrition and Water

Experimental studies have established that the special monkey chow pellets produced by the Purina Company will maintain rhesus monkeys in a healthy condition for a year without further supplementation and with distilled water as the only fluid. The number of pellets and the quantity of distilled water required by unrestrained rhesus monkeys for a 12-month period have been established.

## Feeding Methods

The Purina food pellets were acceptable to the monkeys. The delivery of these pellets to the animals via a spring-loaded hopper or via a zippered plastic tube has been tested over a period of some months, and both methods were effective. A spring-loaded hopper fully loaded with 110 lb of pellets was put through a Saturn IV lift-off simulated vibration without disintegration of the pellets.

## Waste Management

A fiberglass wicking material treated with phosphoric acid has been shown to be an effective absorbent and deodorizer for monkey feces and urine over a long period of time. Rhesus monkeys kept for 6 months in a cage and subjected to a laminar air flow of 1 ft/sec, which would be used in flight to blow feces and urine onto the wicking material, remained in good health, and their blood chemistry and hematology remained normal throughout this period.

## Cage Size

The cage size recommended for the OPE was 25 ft<sup>3</sup> for each animal, with a diameter of 34 in. and a height of 48 in. This is a fairly generous allowance and could possibly be reduced, although it is important not to use too small a cage, which could produce hypokinesia. Federov (ref. 3) has stressed the role which hypokinesia plays in the deconditioning of the body, especially the cardiovascular system.

Through the above studies, the problems involved in flying unrestrained rhesus macaque monkeys have been investigated, and the feasibility of the OPE has been demonstrated. It would be a most appropriate experiment to fly on the Biomedical Experiment Scientific Satellite (BESS).

## REFERENCES

1. Jones, Walton L.: Orbiting Experiment for Study of Extended Weightlessness. NASA Document T-009, 1969.
2. Valerio, David A.: *Macaca mulatta*-Management of Laboratory Breeding Colony, Academic Press, 1969.
3. Federov, B. M.: Proceedings of the 24th International Astronautical Congress, Baku, U.S.S.R., 1973.

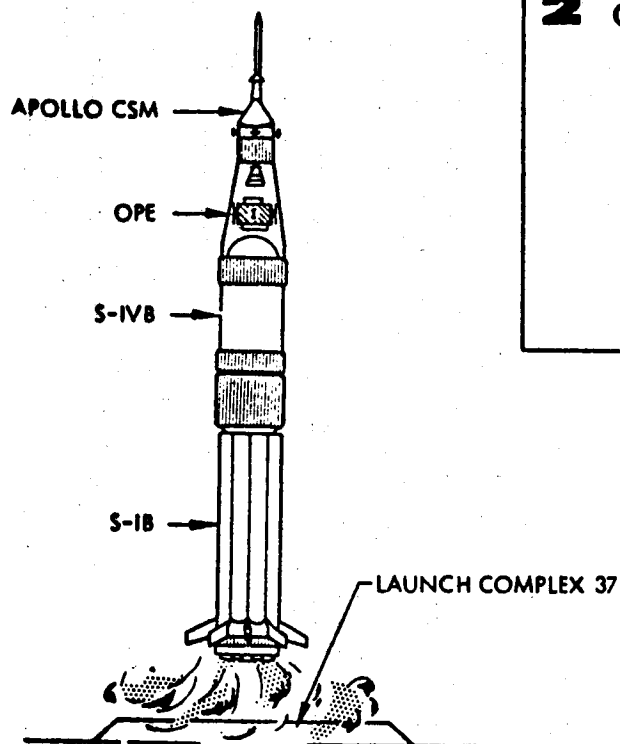
TABLE 1. – BIRTH DATA

Year	Number of births			
	Male	Female	Unidentified Sex	Total
1970	9	4	1	14
1971	14	7	2	23
1972	13	13	2	28
1973	19	13	0	32
1974	33	25	2	60
Total	88	62	7	157
Live births				
Total conceived:	157			
Total live births:	139			
Aborted or stillborn:	18			
Aborted or stillborn:	11.5 percent			

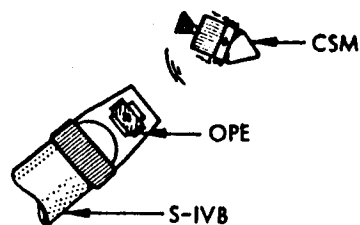


Figure 1.— Female rhesus monkey and young.

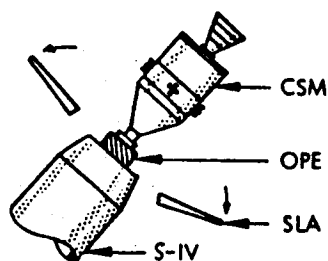
## 1 Launch



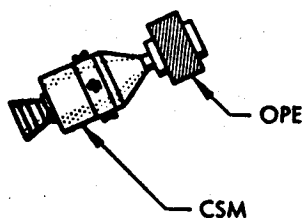
## 2 CSM Separation And Transposition



## 3 Docking



## 4 Transfer to Experiment Orbit



## 5 OPE Separation

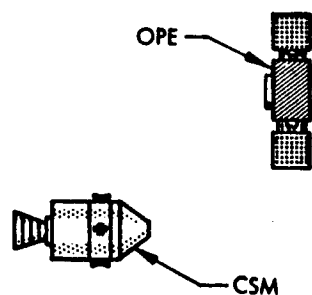


Figure 2.— Proposed launch operations sequence for the OPE. (From Lockheed Company's report to Langley Research Center. NASA document CR 06520, January, 1968.)



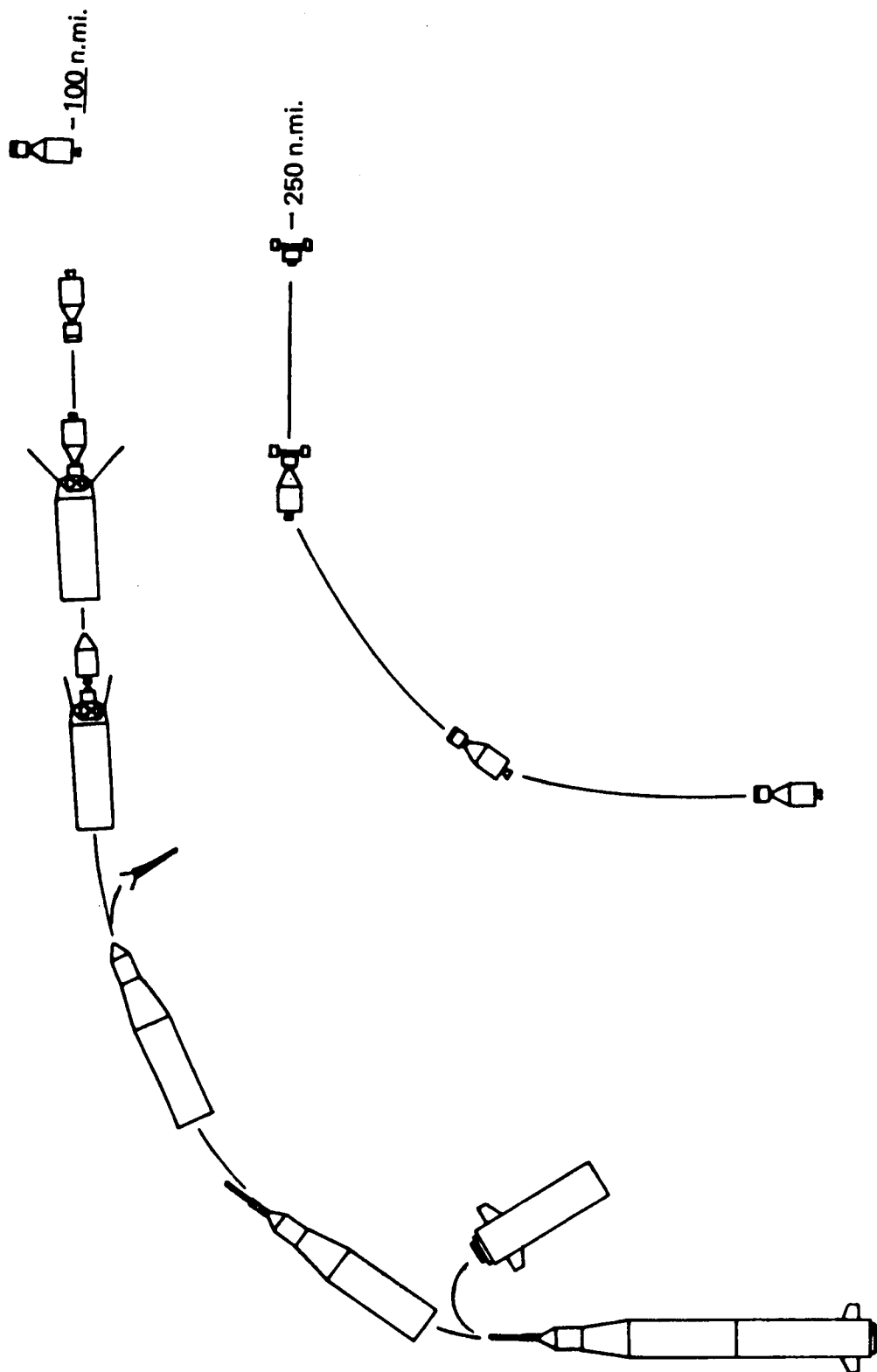


Figure 3.— Launch sequencing phases for the OPE. (From Northrop Company's report to Langley Research Center. NASA document CR 66511, December, 1967.)

## Orbiting primate spacecraft

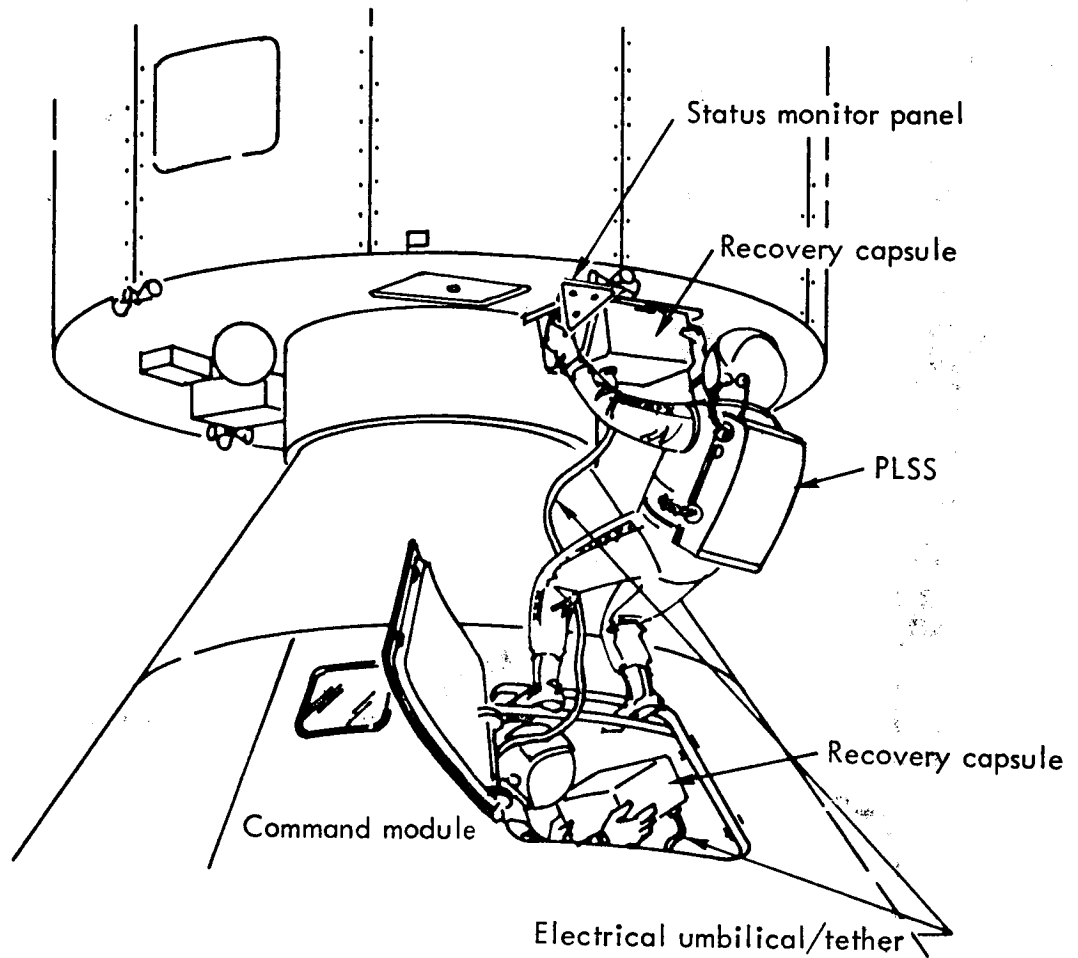


Figure 4.— EVA retrieval of the recovery capsule. (From Northrop Company's report to Langley Research Center. NASA document CR 66507, December, 1967.)

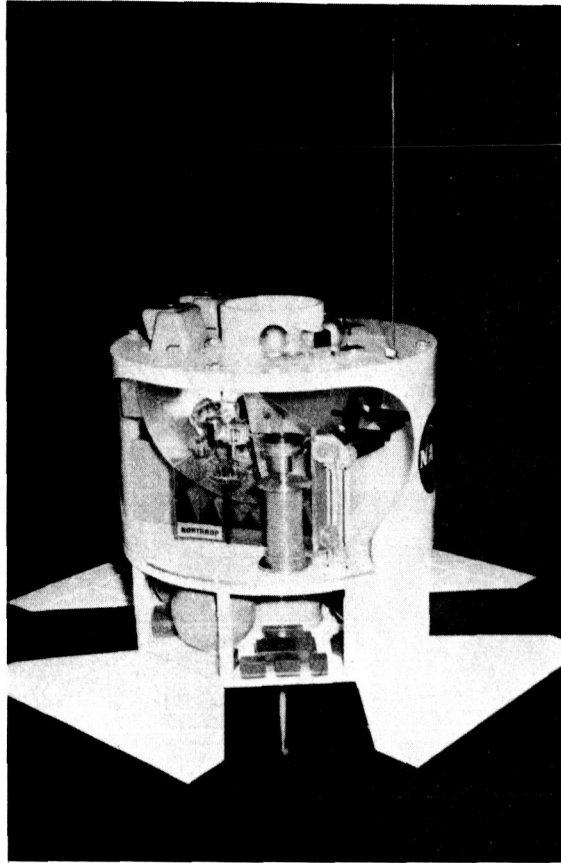


Figure 5.— Model of the OPE spacecraft as designed by the Northrop Company. Capture and transfer canisters for each monkey can be seen at top right. In center foreground is the feeding device. To the left of the feeding device is one of the animal chambers. The toy monkey in the chamber is disproportionately large.

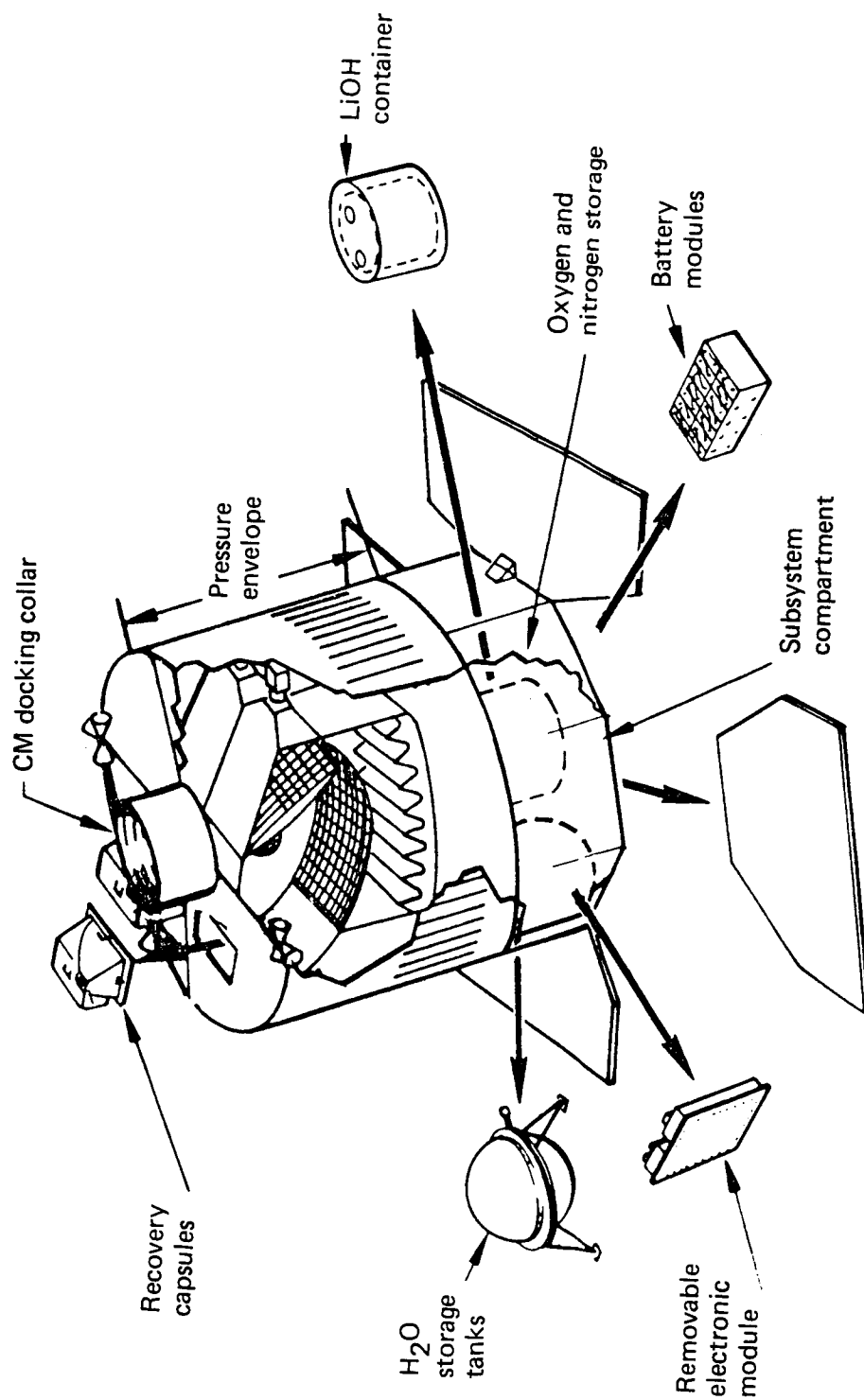


Figure 6.— Primate Spacecraft configuration. (From Northrop Company's report to Langley Research Center. NASA document CR 66511, December, 1967.)

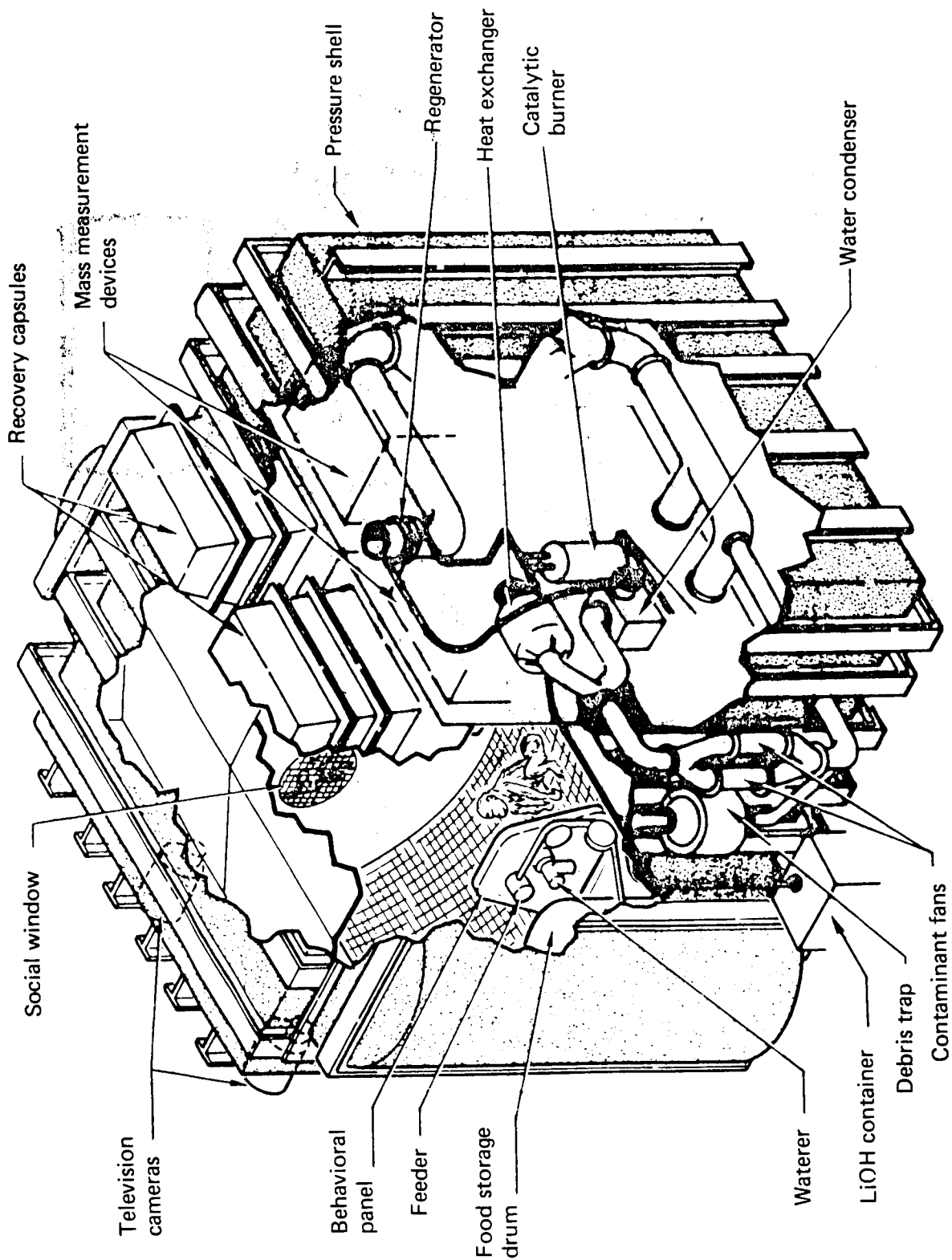


Figure 7.— Primate/Life Cell Interface. (From Northrop Company's report to Langley Research Center. NASA document CR 66510, December, 1967.)

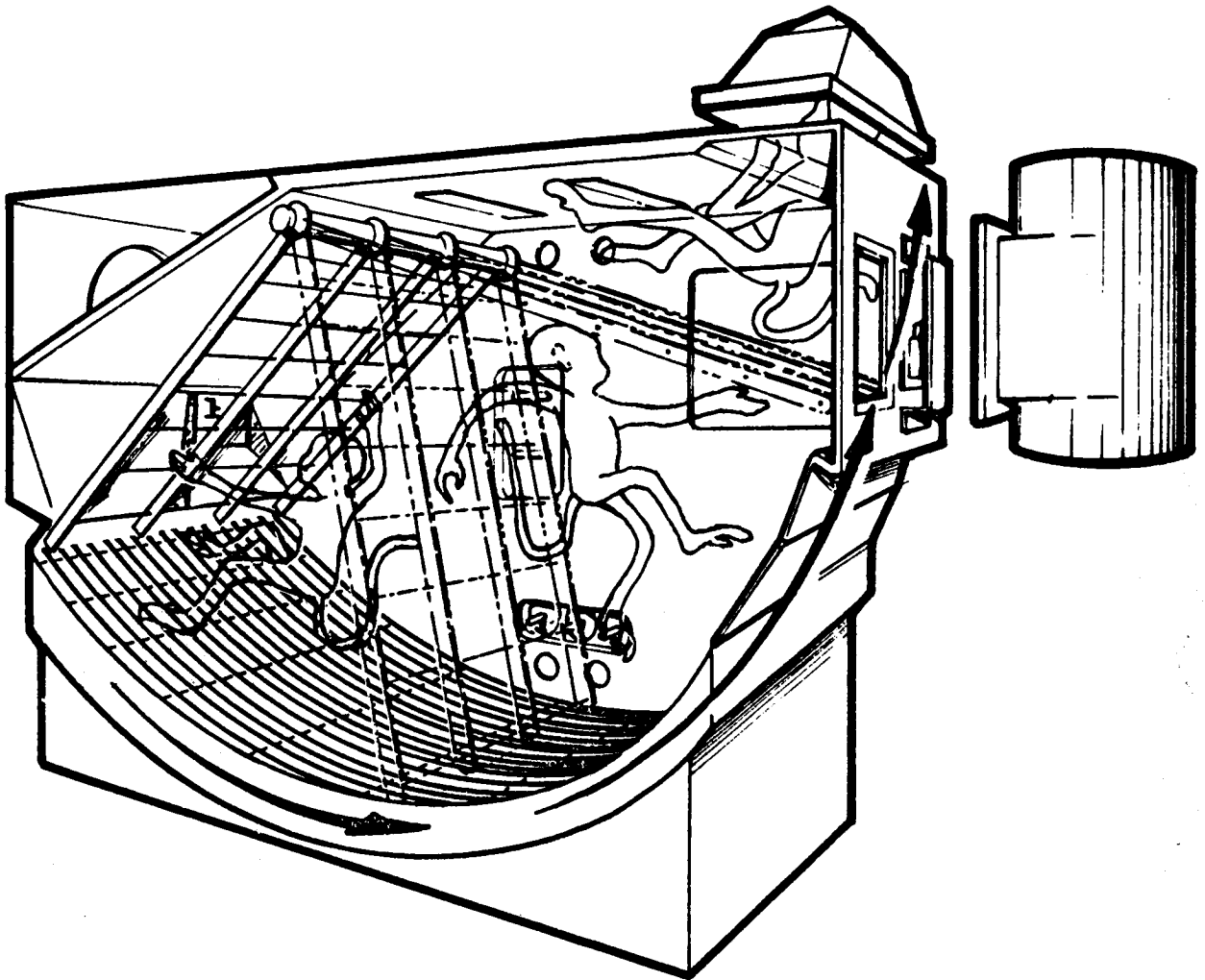


Figure 8.— Northrop primate recovery/mass determination sequence. (From Lockheed Company's report to Langley Research Center. NASA document CR 112017, February, 1972.)

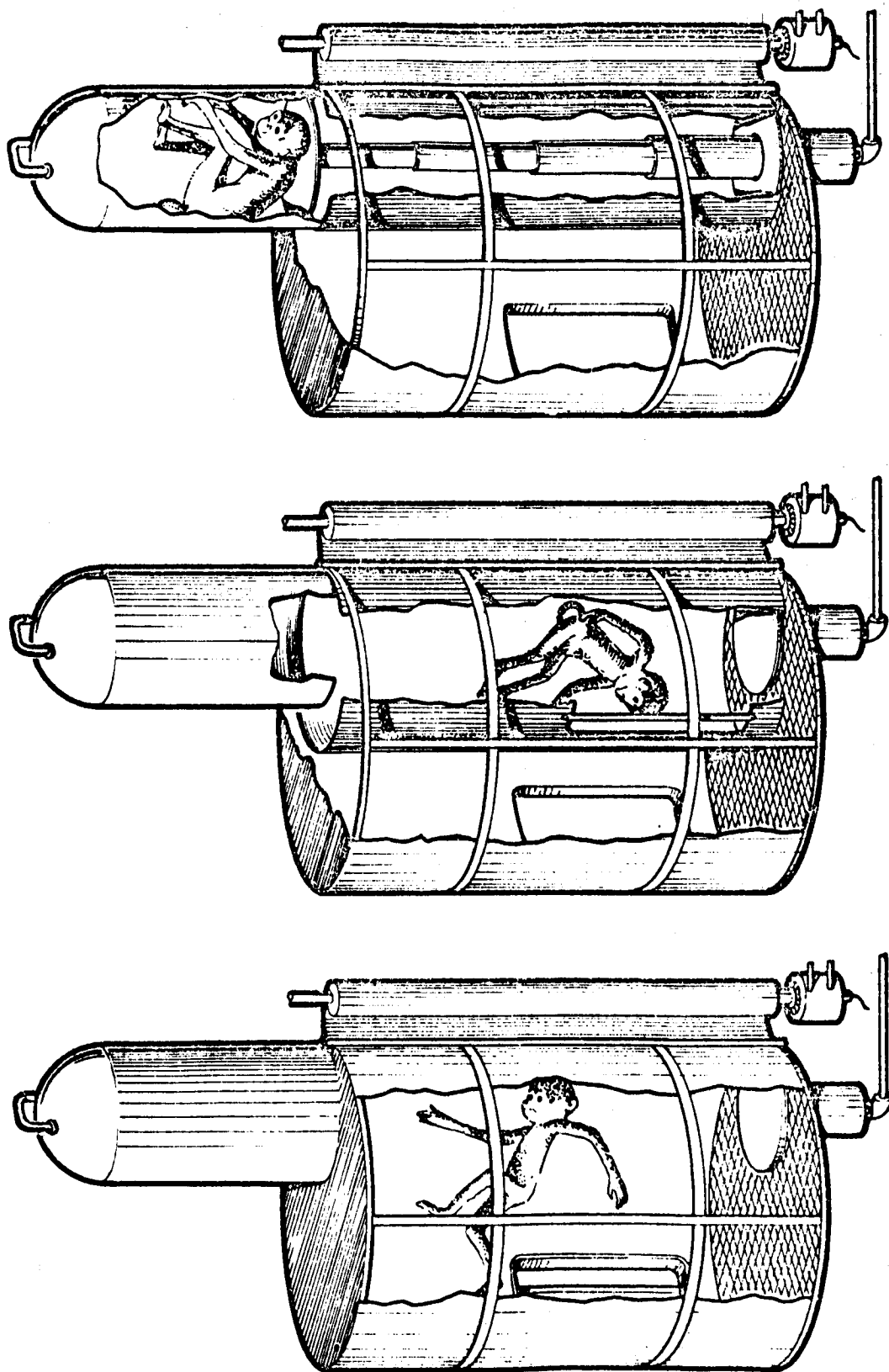


Figure 9.— Lockheed monkey retrieval system. (From Lockheed Company's report to Langley Research Center. NASA document CR 112017, February, 1972.)

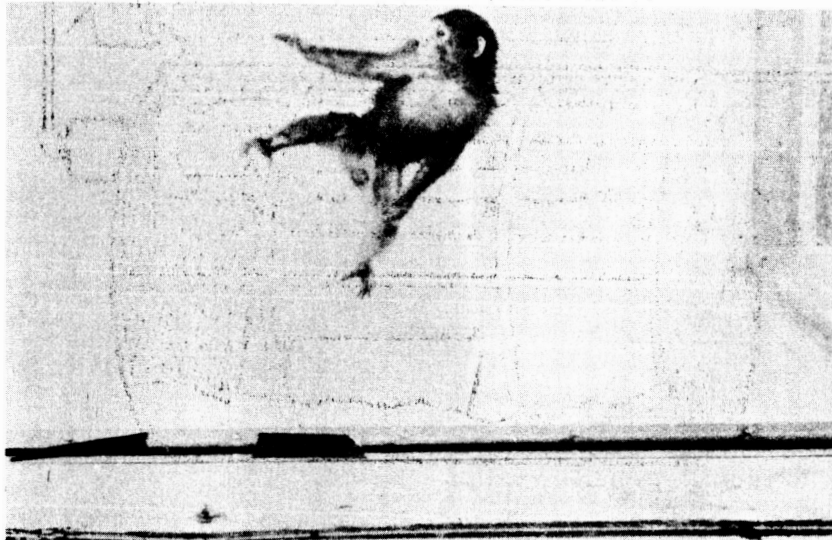


Figure 10.— Young rhesus monkey in the weightless state in an aircraft flying a Keplerian trajectory.

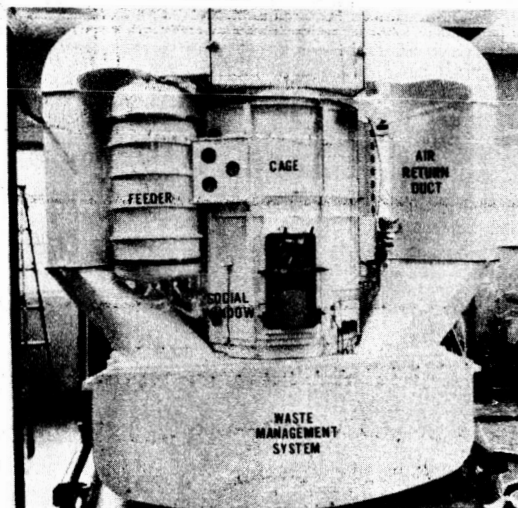


Figure 11.— Technical feasibility demonstration model of the OPE life support system.





Figure 12.— Test facility for exposing monkeys to the air flow necessary for waste management in space.  
The laminar flow is demonstrated by the line of cigarette smoke.

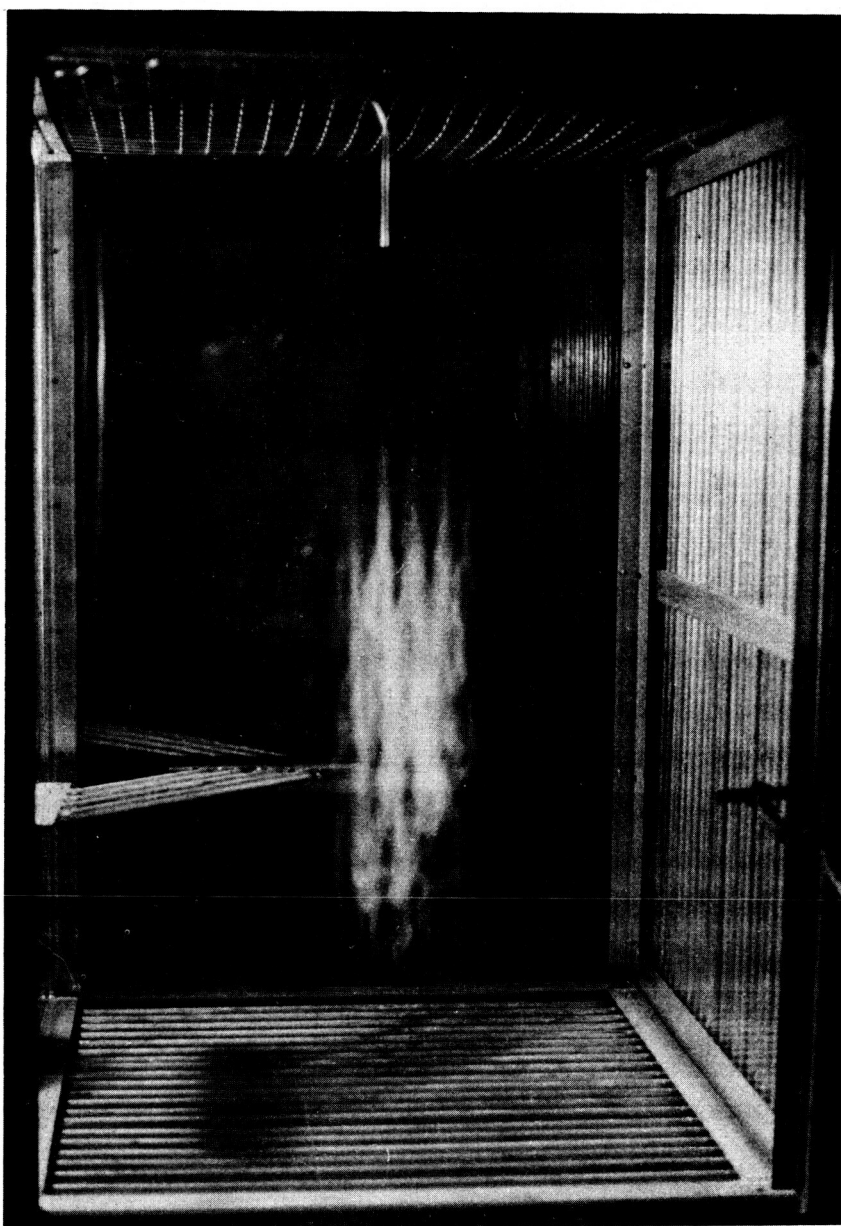


Figure 13.— Test facility for exposing monkeys to the air flow necessary for waste management in space.  
A series of smoke lines in laminar flow.

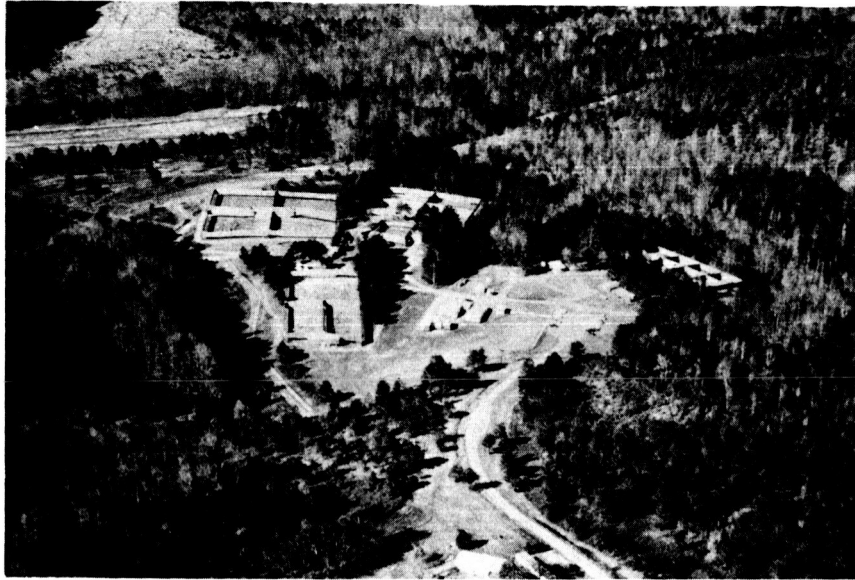


Figure 14.— Yerkes Primate Center Field Station — aerial view. Compounds for breeding NASA monkeys for space research can be seen in center foreground.

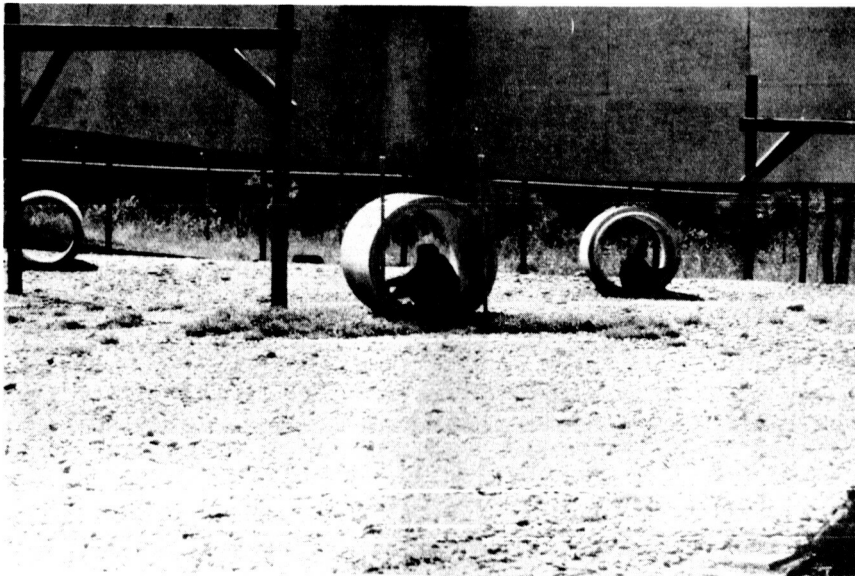


Figure 15.— Interior of NASA breeding compound. Wire and sheet metal construction of the wall of the compound can be seen. Also visible are climbing structures and cement culverts which provide shelter from inclement weather if the animals do not want to go into their sleeping quarters.

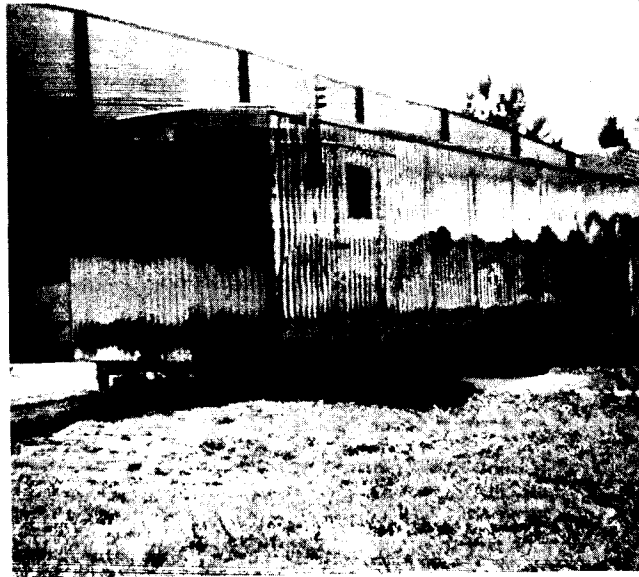


Figure 16.— Monkey sleeping quarters attached to the side of the breeding compound.



Figure 17.— Modified corn cribs for young male monkeys harvested from the breeding compound.  
Heated sleeping quarters are shown attached to the left of the corn crib.

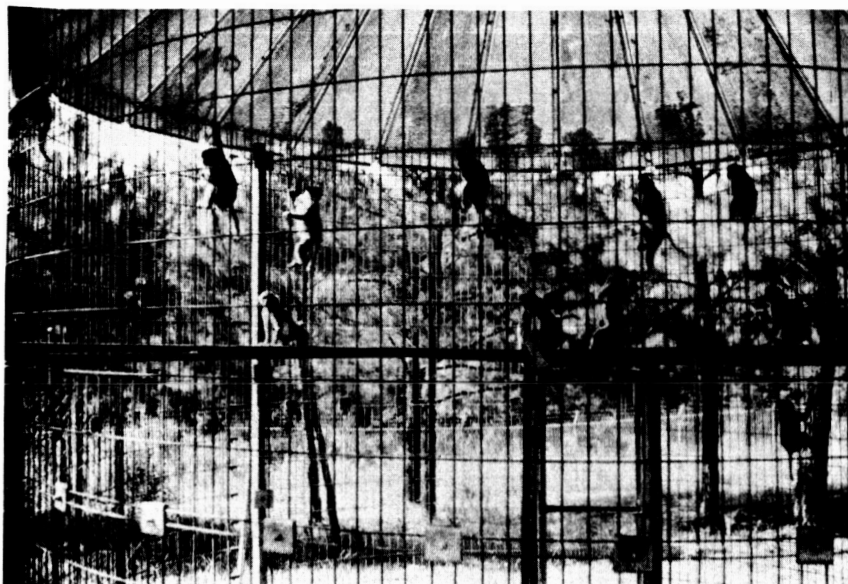


Figure 18.— Closer view of corn cribs with animals in them.

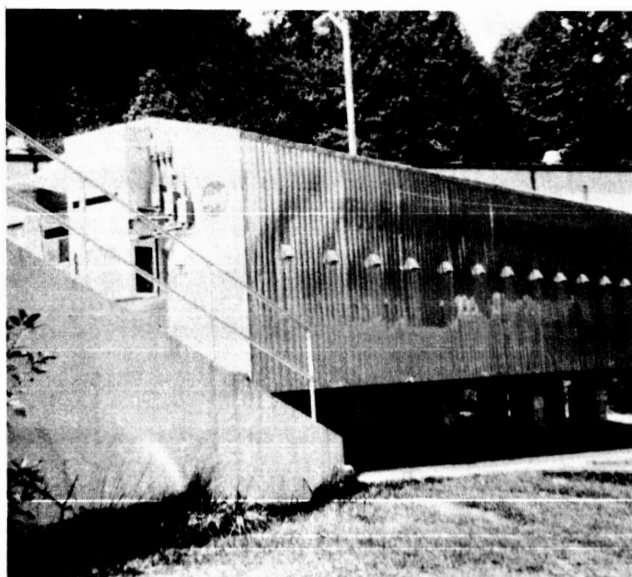


Figure 19.— Conditioning facility at main Center. After a year in the gang cages at the Field Station, monkey flight candidates come to the main Center for conditioning.

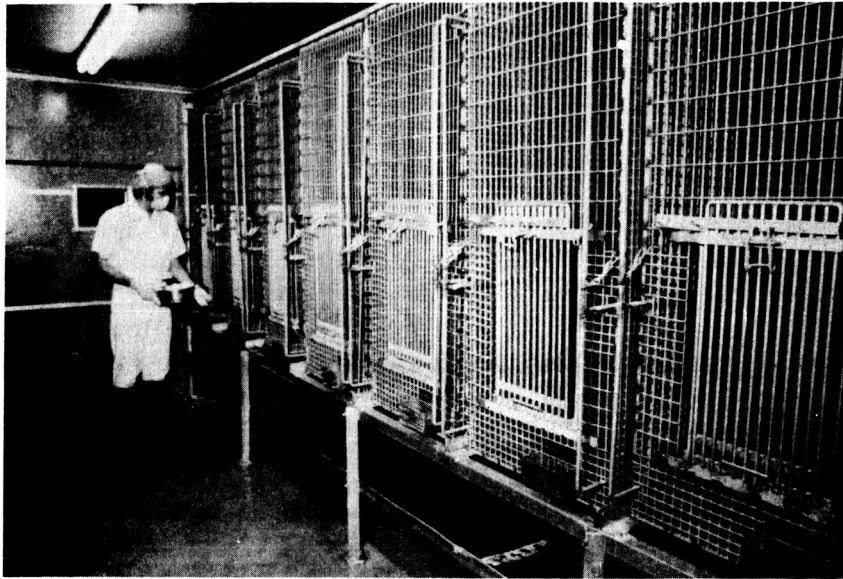


Figure 20.— Interior of conditioning facility at main Center.

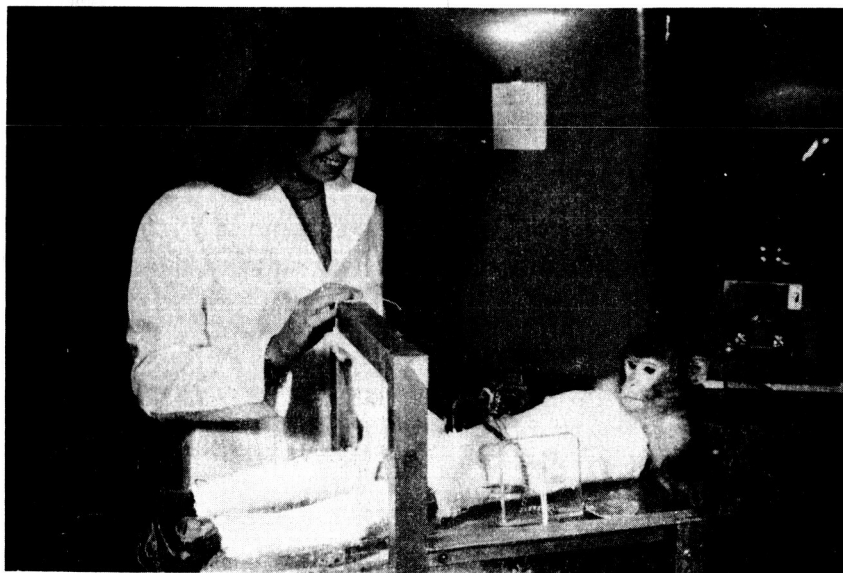


Figure 21.— Monkey inactivated in whole-body cast receiving attention from technicians.



Figure 22.— Monkeys inactivated in whole-body casts grooming each other.



Figure 23.— After 6 months of inactivation, one animal showed cardiac pathology. This section shows invasion of the cardiac muscle fibers by fibrous tissue which shows black in the photograph.



Figure 24.— Vacuolar degeneration of the cardiac muscle in an animal inactivated for 6 months.



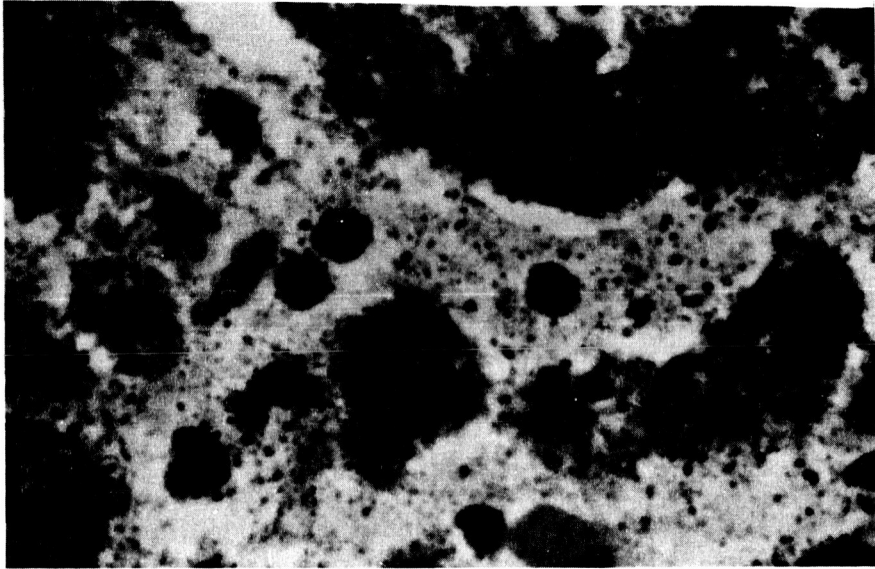


Figure 25.— Destruction of liver cells in animal inactivated for 6 months. Cell debris can be seen between the cords of liver cells.

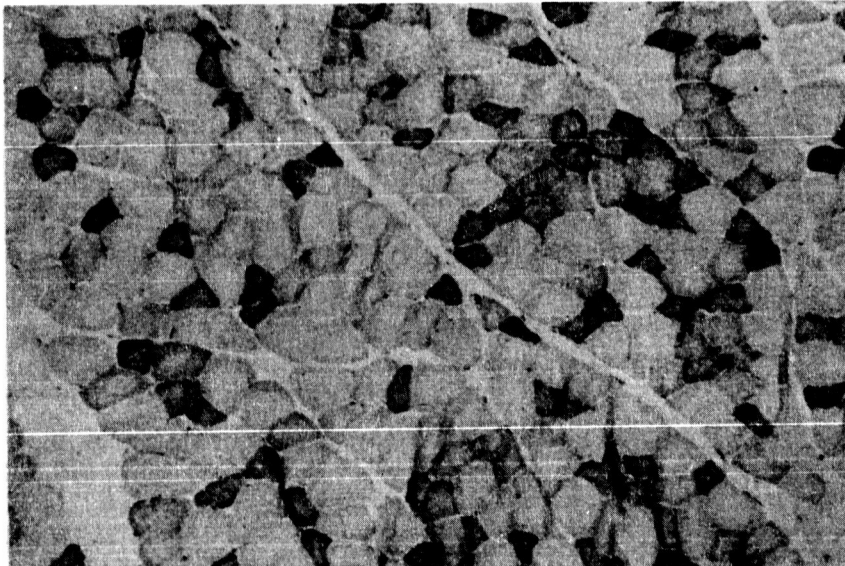


Figure 26.— Decrease in size of type I (oxidative) fibers in skeletal muscle from leg. This was found in all inactivated monkeys. (Type I fibers are the dark fibers in the photograph.)

# CARDIOVASCULAR STUDIES IN THE RHESUS MONKEY

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and

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## INTRODUCTION

Cardiovascular studies in *Macaca mulatta* have been primarily limited to the measurement of blood pressure (refs. 1–4) or, sometimes, blood flows (refs. 5–9) in acute experiments or in short-term chronic experiments. Other experiments involving the chronic measurement of the electrocardiograms (ref. 10) have been conducted, as well as some experiments on myocardial infarction (ref. 11). The selection of an experimental subject for cardiovascular studies of the cerebral circulation is based on an analogue that would best represent the human being. Selection criteria would encompass such areas as (i) primary cerebral blood supply through the internal carotid arteries, (ii) basic intracranial flow distribution similar to the human's, (iii) normal upright posture to investigate reflex changes of the cerebral vascular bed, and (iv) responsiveness to changes in carbon dioxide and oxygen tension in arterial blood. Based upon these criteria, the *Macaca mulatta* has been chosen as the analogue of the human in the study of the cardiovascular system, particularly the control of the cerebral vascular bed.

## SURGICAL PREPARATION

The measurement of cerebral blood flow in the monkey was accomplished by the implantation of a Doppler flow probe around the common carotid artery, with the external carotid artery ligated. Since the internal carotid arteries supply the majority of cerebral flow, this approach fulfilled one of the criteria that was established for this preparation. An incision was made from the angle of the mandible diagonally down the neck. The underlying muscles were separated to expose the carotid artery. The carotid was dissected free from the midneck level to the bifurcation of the internal and external carotids. The external carotid was carefully lifted up and doubly ligated. The flow probe was placed around the artery in the midcervical region, as shown in figure 1. The skin incision was closed and the lead wires from the flow probe buried on the ventral surface of the animal's neck, as can be seen in figure 2. All succeeding experiments were conducted 2 weeks following the surgical implantation. During the recovery period, great care was exercised to ensure that the skin incision area was not inflamed and that the animal had not torn open the incision. This has happened in a few instances, because the monkey, being a very curious animal, will pick at any strange material on his body.

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Measurement of cerebral blood flow must be free of any large amount of extracranial flow contamination, such as flow to muscles of the head or to any other source. In the initial phase of this work, this was taken into consideration in several ways. Flow probes were implanted on the middle cerebral artery. The changes measured from this end artery were compared to a flow probe on the internal carotid artery (ref. 12). The direction of change of the flow was always the same. This meant that measurement of internal carotid artery flow was a good representative site for the detection of changes in cerebral blood flow patterns. Comparisons also were made with isotope washout curves; and, again, the same pattern was found. Figure 3 shows the differences in flow through the internal carotid as compared to the common carotid in the same animal. It is clear that, as pressure was increased, the flow in the common carotid decreased dramatically while internal carotid artery flow remained almost constant. Since the internal carotid in the monkey is very short, it was decided that ligation of the external carotid with probe placement on the common carotid would be sufficient to measure cerebral flow. In determining the possible contaminate channels from this approach, cerebral angiograms were used, as were acrylic casts of the cerebral vasculature. The only source of possible extracranial contamination was found to be the ophthalmic artery. This small vessel could not have received more than 10 percent of the total flow through the internal carotid artery. Other investigators have found that the ophthalmic vascular bed and carotid vascular bed will respond in a similar manner to various stimuli (refs. 13 and 14).

Implantation of a flow transducer around the common carotid artery with the external carotid ligated does represent a good measurement of cerebral blood flow (ref. 15). This preparation can be easily attained in the monkey and maintained for relatively long periods of time. Therefore, the relationship between cerebral flow and arterial pressure, as an example, can be investigated in this analogue.

## RESULTS AND DISCUSSION

### Response to Changes in Arterial Pressure, Oxygen, and Carbon Dioxide

One of the classical properties of the cerebral vascular bed is termed "autoregulation" or the relationship between cerebral flow and arterial pressure. This relationship can be seen in figure 4. As arterial pressure is raised or lowered, the cerebral flow does not change within certain limits. At some critical pressure level, the flow will begin to decrease and approach zero flow in a fairly linear fashion beyond the critical pressure level. The property of autoregulation has been thought to be myogenic in most vascular beds. In the cerebral vascular bed, this also appears to be true (refs. 16 and 17). Another property can also be seen in this figure: Beta-adrenergic blockade has no effect on the autoregulatory curve. The blocking agent was given intravenously. This implies that many drugs do not cross the blood-brain barrier, thus, common agents used to study the circulatory bed in other organs cannot be used in the same way in the brain. The major implication from this figure concerns the location of the vascular receptors. The receptors, both alpha and beta, appear to be located on the brain side of the barrier. Thus, for any response to occur in the vascular bed, the substance must cross this barrier to act on the vascular smooth muscle.

Two substances that readily cross the blood-brain barrier and are effective on the cerebral blood flow are oxygen and carbon dioxide. The level of oxygen in arterial blood has to be lowered a significant amount before any change in cerebral flow occurs. Changes in cerebral flow and

arterial pressure to an exposure of 5 percent oxygen can be seen in figure 5. As the time of exposure increases, cerebral flow also increases; thus, implying a progressive cerebral hypoxia. It must be recognized that the flow increase observed with low oxygen may well be the result of changes in the metabolic activity of the brain. In the above condition, the cerebral venous oxygen content goes down dramatically. The difference in oxygen across the brain becomes small. Metabolic oxygen consumption remains fairly constant, thus the flow increases to meet the demand. Restoration to room-air breathing returns the flow toward, and eventually to, control levels.

Cerebral flow has been found to be very sensitive to changes in the arterial level of carbon dioxide. The change in flow, in man and animals, is linear with changes in arterial carbon dioxide (refs. 18 and 19). The normal relationship can be found in figure 6. As the arterial carbon dioxide was increased in the monkey, a linear increase in flow was found. The slope of this relationship is very near one. How does a change in arterial carbon dioxide affect the autoregulation relationship? The shaded curves of figure 7 show this relationship. The curves were obtained from lower to upper curves, respectively, at room-air, 6 percent, 9 percent, and 12 percent inspired carbon dioxide levels. At each successive level of inspired carbon dioxide, the flow increased at normal pressure, but autoregulation was still present until the 12 percent level was attained. At this high level, autoregulation was almost lost. This flow level, at which autoregulation will occur, seems to be influenced by the level of carbon dioxide. The metabolic effect of carbon dioxide in the vascular smooth muscle has been felt to be through a hydrogen ion effect. As metabolism of the brain changes, local hydrogen ion concentration can easily change the flow in a given area; thus, a local regulatory scheme can be attained.

#### Innervation of Cerebral Vessels

For many years, it was believed that the innervation present in the cerebral vessels had no real functional significance in any physiological sense. Early work demonstrated the effect of catecholamines on the surface of the pial vessels (refs. 16 and 17). However, when these same catecholamines were administered into the carotid artery, there was no effect on cerebral blood. In other animals, a rich adrenergic innervation had been shown by histochemical techniques to be present on the adventitial surface of the cerebral vessels (refs. 20 and 21). This innervation could be followed along vessels that ranged in size from the basilar artery down to small arteries of 500  $\mu\text{m}$  in diameter. Whether the intraparenchymal vessels receive an adrenergic innervation is not really known at present.

The role of the sympathetic innervation of the cerebral vessels on cerebral flow and autoregulation was investigated in the monkey. This was accomplished by the implantation of Doppler flow probes on both the carotid arteries and removing one superior cervical ganglion. Therefore, each animal served as its own control. Comparison of the flows through the two sides showed that the denervated side had a larger flow (ref. 22). The increase in flow of the denervated side over the normal side was 34 percent in all animals studied. Figure 8 shows that autoregulation was still present in the denervated portion of the cerebral vascular bed. This indicated that the sympathetic fibers to the cerebral vessels were maintaining some sort of tension in the vessel wall and that removal caused a vascular dilation on the denervated side. However, removal of the superior cervical ganglion may not have eliminated all of the adrenergic nerves to the cerebral vessels in the monkey. As blood was being withdrawn from the animal to determine the pressure range of autoregulation, we noticed that, upon reinfusion, the response of the denervated side differed from the normal.

Figure 9 shows the reinfusion loop from a representative animal. This figure indicates that, with the same stimulus, namely reinfusion of blood, the area encompassed by the loop was much greater in the denervated side. The same result has been found in denervated skeletal muscle bed and indicates a loss of some stiffness component from the vessels (ref. 23). The loss of sympathetic innervation, therefore, would lead to this result. Bilateral denervation was also accomplished in another group of animals (ref. 24). The results of autoregulation still being present was similar to the above study. We did find that the sensitivity to carbon dioxide was decreased in the denervated animal, when compared to the normal animal. This unexpected result could be explained through the blockade of the release of norepinephrine by hydrogen ions in the normal animal. Loss of norepinephrine would indicate that there was some direct effect of carbon dioxide on smooth muscles and the two effects were additive.

Direct demonstration of the adrenergic and cholinergic innervations of the cerebral vessels was lacking in the *Macaca mulatta* monkey. We were still uncertain as to the direct effect of removal of the superior cervical ganglion. Figure 10 shows the histochemical fluorescence of catecholamine on the middle cerebral artery of the monkey. Close inspection of this picture will demonstrate the typical varicosity that others have shown. This pattern has been found on the basilar, vertebral, and most of the major vessels around the circle of Willis. Removal of the superior cervical ganglion was found to eliminate all visible signs of any adrenergic innervation, with the exception of a very few fibers that may arise from an intracranial source. We have found adrenergic fibers on most vessels in sizes of slightly less than 500  $\mu\text{m}$ , but have not found innervation of vessels as they course into the substance of the brain.

The cholinergic innervation of cerebral vessels in the monkey appears to be slightly less dense as compared to the adrenergic innervation. In the histochemical determination of cholinergic fibers, care must be taken to ensure that substances other than the cholinergic nerves were not being stained. We have been able to find routinely cholinergic fibers in the absence of adrenergic fibers on the cerebral vessels. Cholinergic nerves coursing in the adventitia can be seen in figure 11. It should be noticed that no varicosities can be found along the length of these fibers. This section was taken from the middle cerebral artery. The distribution of these fibers was found to be almost identical to the adrenergic supply. We have not attempted to utilize both techniques in the same preparation, but would anticipate that the two fiber groups course together over the surface of the vessel. Again, we have found these cholinergic fibers on vessels in sizes down to 500  $\mu\text{m}$ .

There are two distinct types of vessels within the cranial cavity (ref. 25). One type is referred to as the extraparenchymal vessels that include the large distributing arteries and the pial vessels. As these vessels penetrate into the substance of the brain, certain histological changes have been observed which have led us to differentiate the second type as the intraparenchymal vessels. Most of the research that has been accomplished has been concerned with the extraparenchymal vessels. Both the nervous supply and reactivity of these vessels were regarded as the only important factor in cerebral blood flow. Recently, this has been strengthened by the finding that the major pressure drop in the cerebral circuit occurs in vessels larger than 300  $\mu\text{m}$ , and the greatest portion of this pressure drop was found in vessels of 1 to 2 mm in diameter (ref. 26). Since the innervation apparatus was found to be most abundant in this size vessel, it is very tempting to speculate that neurogenic control of cerebral flow resides in the larger vessels and that the local effects were dominant in vessels less than 300  $\mu\text{m}$  in diameter. Irrespective of such speculation, the important point is that both sympathetic and parasympathetic nerves were coursing over the adventitia of cerebral arteries. This dual innervation offers many methods for active changes in vessel caliber.

## Cerebral Flow Response to Acceleration

Acceleration stress is encountered in any space flight activity that involves the human being. One of the common features of increased gravitational stress is the tendency for a reduction in arterial pressure (ref. 27). In most instances, the reflex control of arterial pressure can maintain the pressure to the point that adequate cerebral perfusion can be attained. As the direction of the acceleration vector is changed so that the major force is directed down the long axis of the body ( $+G_z$ ), the reduction in arterial pressure becomes an exceedingly important problem. The higher the level of  $+G_z$  acceleration, the more the reflex activity has to change to maintain an adequate driving pressure for cerebral flow. Cerebral flow studies during  $+G_z$  acceleration stress have not been accomplished, because of the lack of a proper method to adequately study the problem under these conditions. With the previous experiment, using the *Macaca mulatta* monkey as background information, we felt that this approach would allow us to initiate studies designed to determine changes in cerebral flow during acceleration stress.

The monkeys that had been previously implanted with a Doppler flow probe around the common carotid artery were placed at the end of a 7.6-m radius centrifuge. A catheter was placed in one femoral artery for the injection of contrast material into the animal and automatic sampling of arterial blood. A solid-state catheter-tip pressure sensor was passed through the opposite femoral artery to the arch of the aorta to measure arterial pressure. Roentgenograms were obtained at each level of acceleration so that the calculation could be made of pressure at the site of probe implantation. Angiograms were taken in separate exposures to determine the movement of the probe in relation to other structures during the acceleration period. A control angiogram can be seen in figure 12, with the flow probe being identifiable around the carotid artery. Figure 13 shows the same animal at  $+3G_z$ . Contrast material was found to still reach the head in this animal which means that there was still some flow of blood to the brain. There was no apparent mechanical stricture of the vessel from the implantation of the probe. Another fact also appears in this angiogram: the downward movement of the aortic arch region. We have observed this phenomenon in other animals and now have found the same type of displacement in the monkey.

Figure 14 shows a comparison of responses to increasing acceleration levels during a 120-sec exposure to the acceleration. With increasing acceleration levels, the heart rate at first increased, but then began to decline. Arterial pressure decreased and the pulse pressure narrowed with each successive acceleration level. This was a consistent finding in all of the animals. Since we were using a catheter-tip pressure sensor, the pressure measured should not be influenced by the acceleration profile and should reflect true changes in the intravascular pressure. Using the roentgenograms, the pressure at the site of implantation of the flow probe and the eye level pressure could be calculated. These values are shown in figure 15. Mean arterial pressure declined from an average of 118 mm Hg to 40 mm Hg at the arch of the aorta with an increase in  $+G_z$  acceleration. The pressure at the site of probe implantation followed the same course, but dropped more severely because of the hydrostatic column effect and the acceleration field. Cerebral blood flow also decreased with the change in acceleration, but an important factor was the relationship between the change in flow and the change in pressure, which can be seen in figure 16. As the pressure at the site of the probe decreased, cerebral flow tended to remain fairly constant over a pressure range of approximately 50 mm Hg. Beyond this level, cerebral flow began to drop rapidly.

The results from this study indicate that the fall in cerebral flow with pressure followed an autoregulatory response curve. The rapid decline in flow at a pressure of approximately 70 mm Hg

agrees with all of the other normal data in the monkey that we have obtained. However, there are two other factors that should be considered before this type of explanation can be acceptable. What has happened to the arterial tension of carbon dioxide during this period? Measurement of the arterial carbon dioxide and oxygen tension showed very little change from their control values. This indicates that change in the blood gases that enter the brain are not contributing to the flow maintenance during the acceleration stress. Since we have demonstrated the presence of both cholinergic and adrenergic nerves on the cerebral vessels, could these be playing a role in the maintenance of flow during acceleration stress? We have found that removal of most of the adrenergic nerves did not eliminate the autoregulation response in control animals but that withdrawal of sympathetic activity does increase cerebral flow. This could explain the maintenance of cerebral flow without the maintenance of autoregulation during acceleration. Yet another neurogenic component could be invoked to obtain vasodilation over this range, and this would be cholinergic vasodilation fibers. The neurogenic component, even though present, has not been shown to be reflexly activated under normal physiological conditions, much less during the stress of acceleration or weightlessness.

### Cerebral Blood Flow and Cerebellar Stimulation

Stimulation of a certain area of the cerebellum has been shown to dramatically increase arterial pressure and has been suggested or involved in the orthostatic reflex adjustment of arterial pressure (ref. 28). With such a reflex increase in arterial pressure, does the cerebral blood flow increase or remain the same as would be expected with the normal autoregulatory response? The monkey is a very good candidate for such an orthostatic reflex since these animals assume an upright posture in their normal daily lives. The second important factor is the ability to obtain rapid, reliable measurement of cerebral blood flow in this animal.

Stimulation of the cerebellum on the monkey was found to produce a rapid rise in arterial pressure, much as has been observed in other animals (ref. 29). A typical response to stimulation can be seen in figure 17. With the beginning of the stimulation, the arterial pressure rises very rapidly; and, the cerebral blood flow was found to increase simultaneously. As the current used for stimulation was changed, both the pressure and flow responses would change. The maximum pressure response in most animals was found at a stimulation intensity of 3.5 mA as seen in figure 18. The flow response followed the pressure response in this regard. When the change in flow was plotted against the change in pressure, a linear relationship was obtained as shown in figure 19. The slope of the flow-pressure curve is 0.4 cc/min/mm Hg-1. This type of linear relationship suggests that the normal autoregulatory response had been abolished. However, we find that this is not the case, but rather autoregulation has just been shifted to a higher flow level. The vasodilation of the cerebral vascular bed with cerebellar stimulation is of neural origin and does involve the cholinergic and/or the adrenergic nerves to the cerebral vessels.

The increase in arterial pressure has been associated with an increase in peripheral resistance and vasoconstriction in most peripheral vascular beds. Vasoconstriction is generally associated with an increase in sympathetic discharge to these regions. In the case of the cerebral vascular bed, a vasodilation was found, which can be either associated with a decrease in sympathetic activity or a vasodilation mechanism associated with the cholinergic fibers. Modulation of cerebral flow activity can be reflexly activated through stimulation of the cerebellum. This fact alone indicates a normal role for the autonomic nervous system in the stability of cerebral flow in the primate.

## CONCLUDING REMARKS

### Summary

In summary, cerebral flow studies are being conducted in the *Macaca mulatta* to characterize the control of the circulation to the brain during various normal and stressful conditions. The ease of handling and maintenance plus the ability to isolate the cerebral flow dictate that the monkey is a prime subject for cardiovascular studies. As far as can be ascertained at present, the analogue to human reactions is very close and we must consider this animal as a good human analogue.

### Other Cardiovascular Studies

Changes in skeletal and cardiac muscle associated with immobilization have been found in the monkey by Dr. Bourne and Dr. Golarz. These changes are degenerative and would indicate that other cardiovascular states may also be changing in a condition that simulate a weightless state. In conjunction with Dr. Bourne and Dr. Golarz, we are beginning to investigate the physiological consequence of the pathological changes they have observed in the heart. These studies are very new and the data too preliminary to realistically discuss at the present time. However, we anticipate that change in the pressure and flow in the circulatory system will be studied in these animals.



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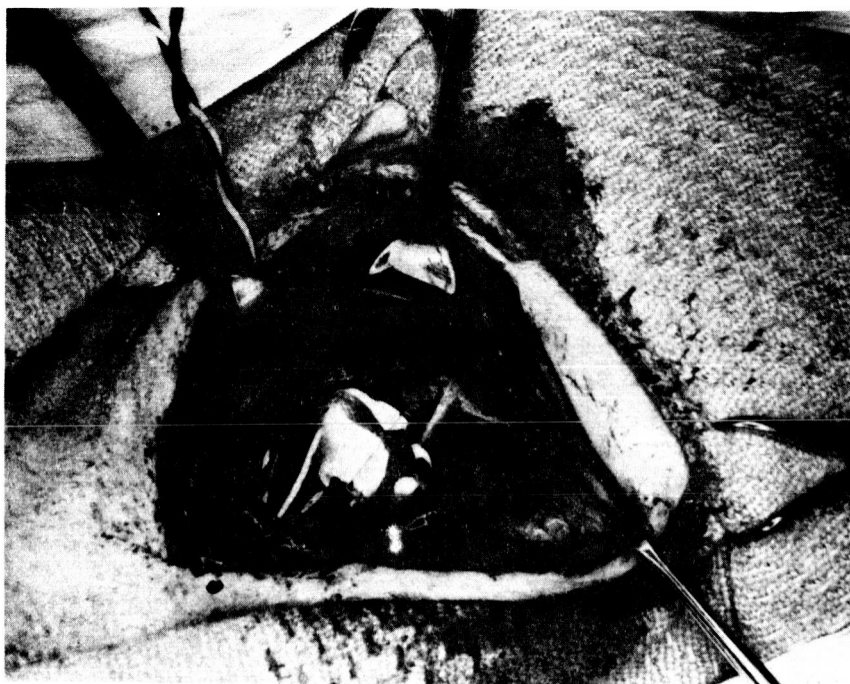


Figure 1.— Implantation of Doppler flow probe around the common carotid artery.



Figure 2.— Skin incision closed with lead wires from flow probe buried under skin, as seen in upper left of figure.

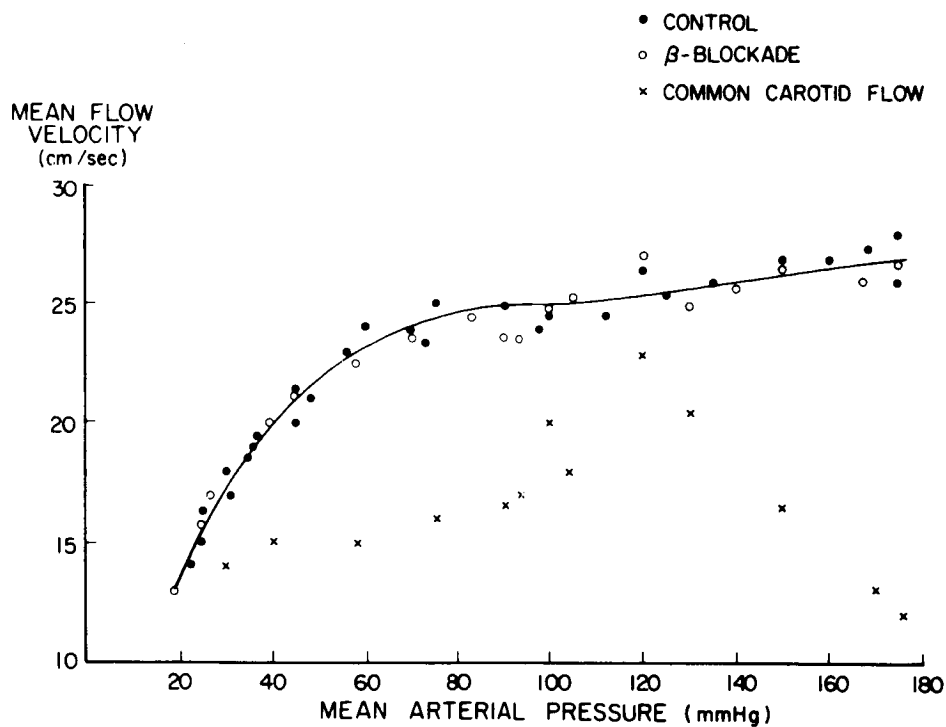


Figure 3.— Changes in mean flow velocity in the internal and common carotid arteries as the mean arterial pressure was varied over a wide range.

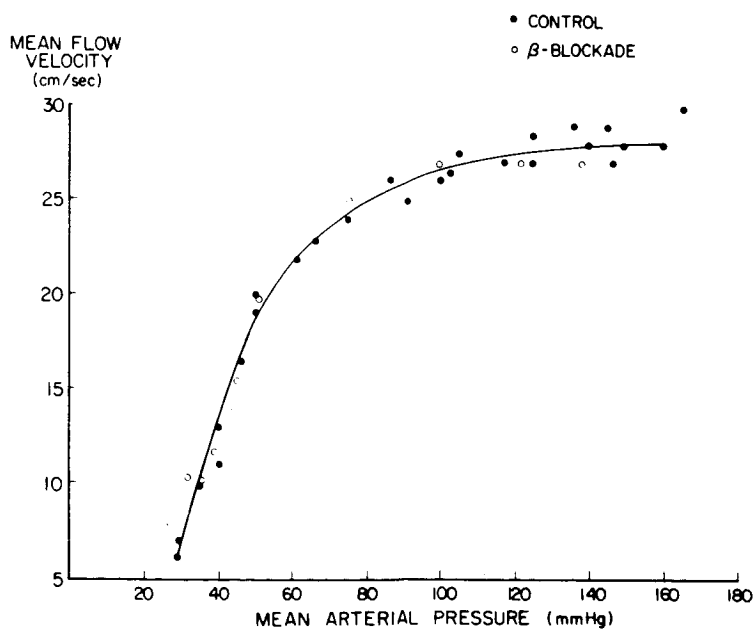


Figure 4.— Mean cerebral flow velocity plotted versus mean arterial pressure. Mean arterial pressure was changed by exsanguination and the infusion of aramine.

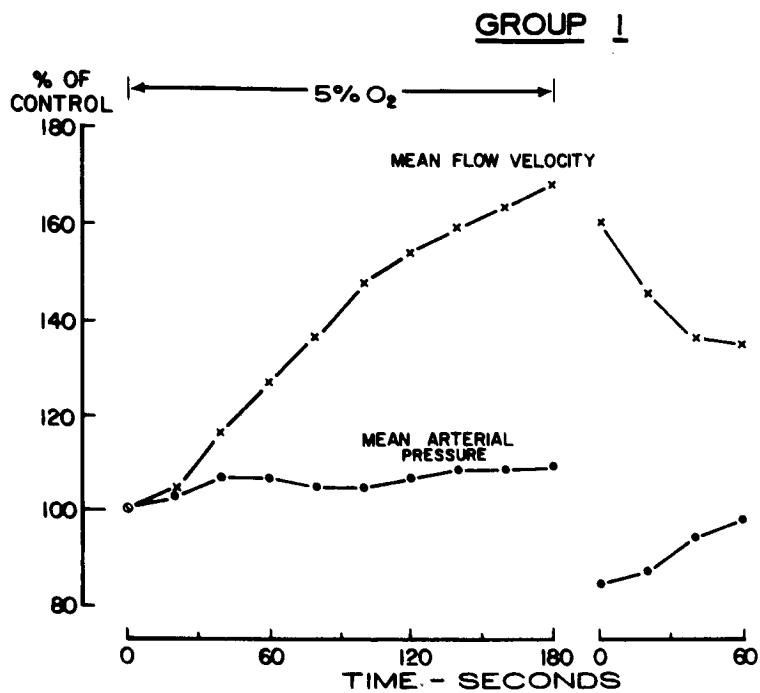


Figure 5.— Percent change in mean carotid flow velocity and mean arterial pressure with time following the exposure of the animal to 5 percent oxygen.

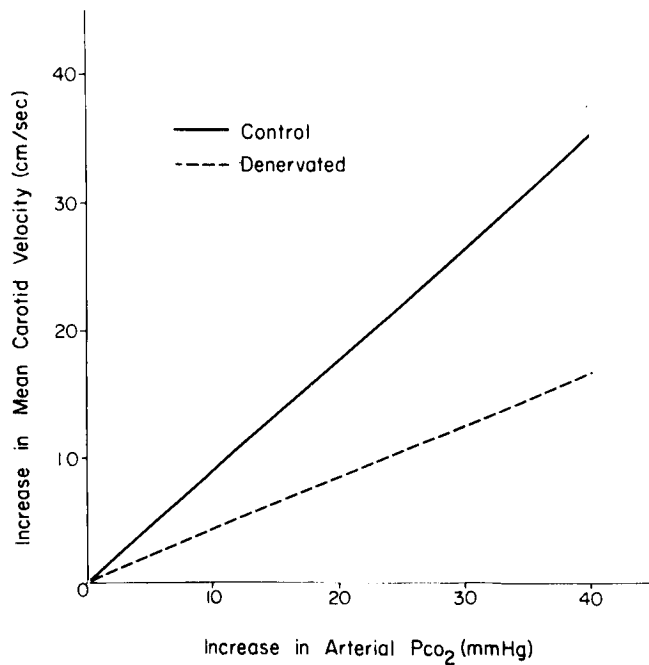


Figure 6.— The relationship between the increase in cerebral flow velocity and the increase in the arterial level of  $P_{CO_2}$ .

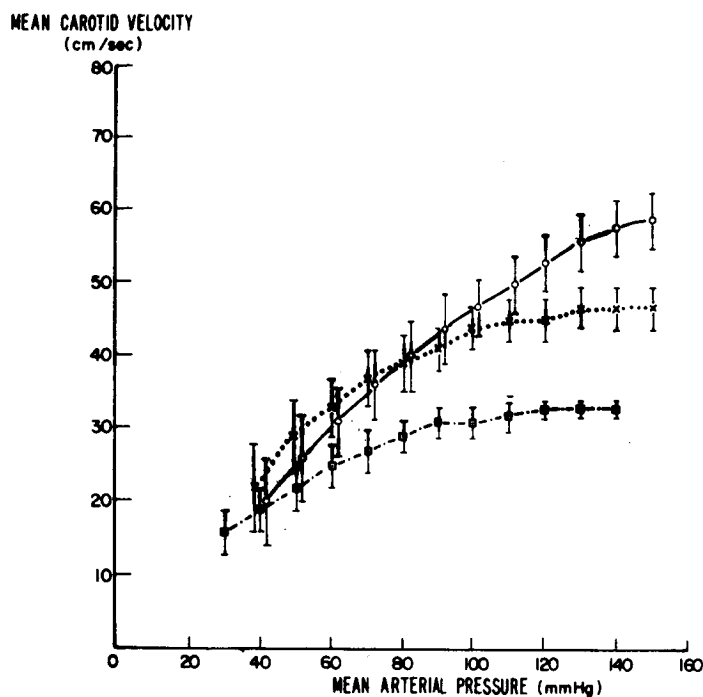


Figure 7.— Mean carotid flow velocity versus mean arterial pressure. Arterial pressure was varied as described in figure 4. The lower shaded curve is the normal autoregulatory curve while the remaining shaded curves were obtained with the animal breathing 6 percent, 9 percent, and 12 percent  $\text{CO}_2$  in air. Shaded area represents one standard error of the mean (SEM).

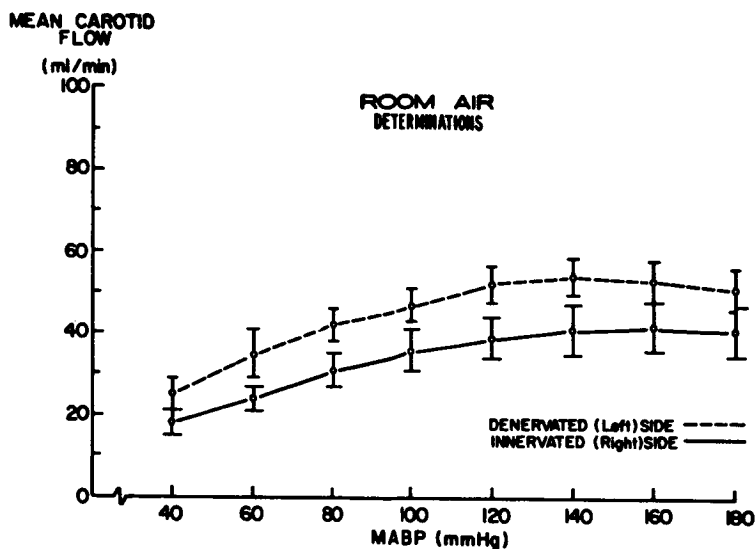


Figure 8.— Mean carotid flow versus mean arterial pressure in a group of animals that had undergone bilateral Doppler flow probe implantation and removal of the left superior cervical ganglion. Bars through the points represent one SEM.

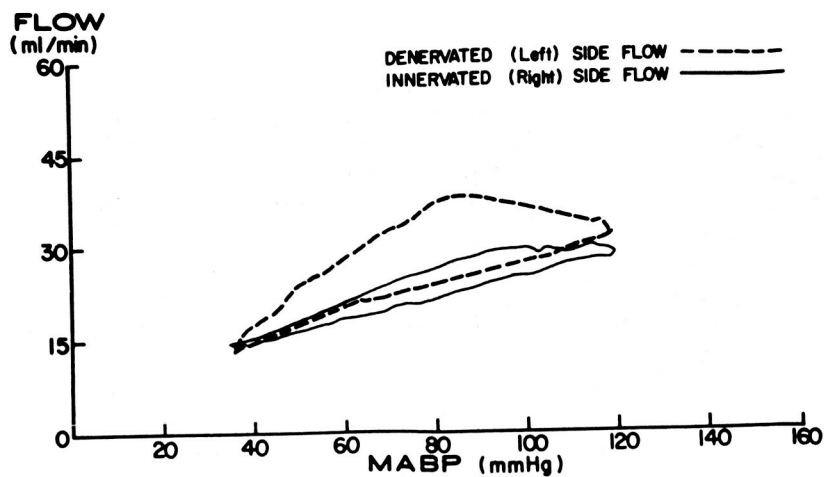


Figure 9.— Mean carotid flow versus mean arterial pressure obtained in a representative animal during reinfusion of blood following exsanguination. Notice the difference in the area encompassed by the two loops.

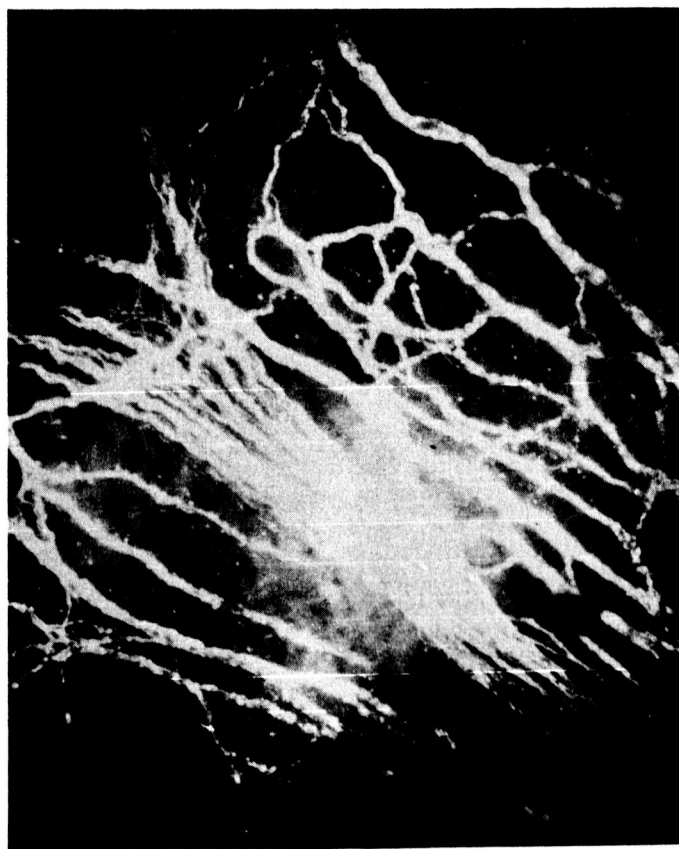


Figure 10.— Histochemical fluorescence of catecholamines in adrenergic nerve fibers located in adventitial layer of middle cerebral artery of the monkey.

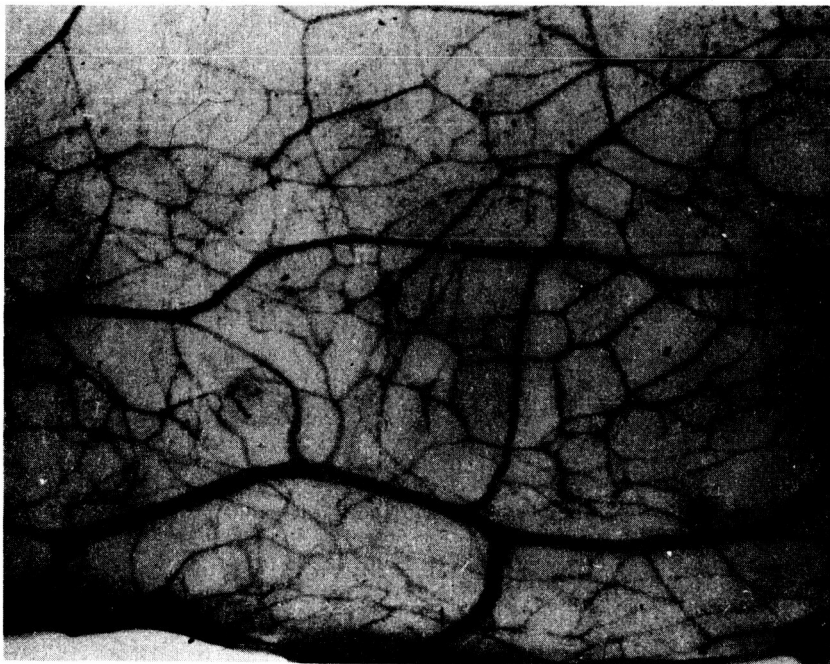


Figure 11.— Parasympathetic fibers located in the adventitial layer of the middle cerebral artery of the monkey.

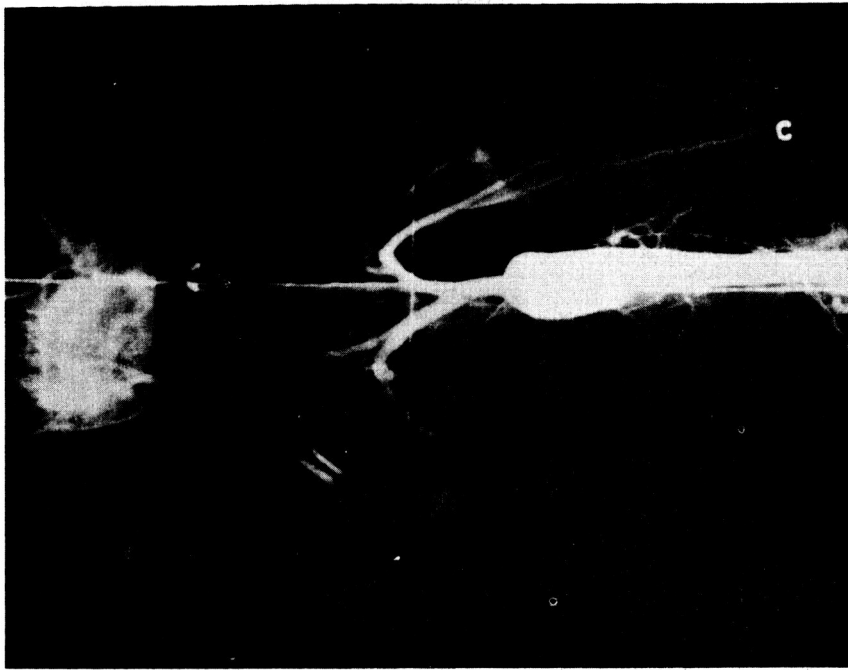


Figure 12.— Angiogram showing the relationship between major vessels and carotid flow probe during control condition.



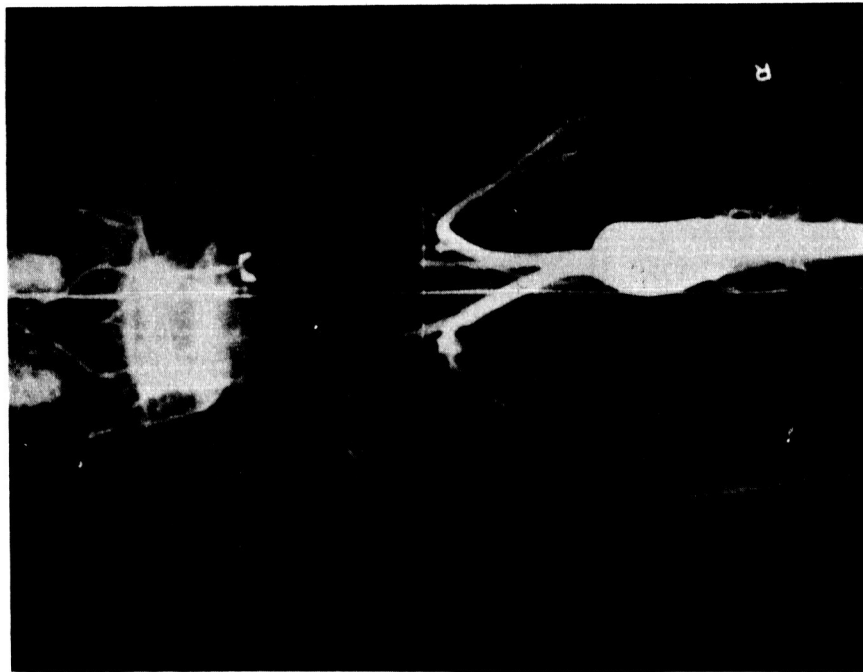


Figure 13.— Angiogram of same animal as shown in figure 12, except now the animal was at +3G<sub>z</sub> acceleration level.

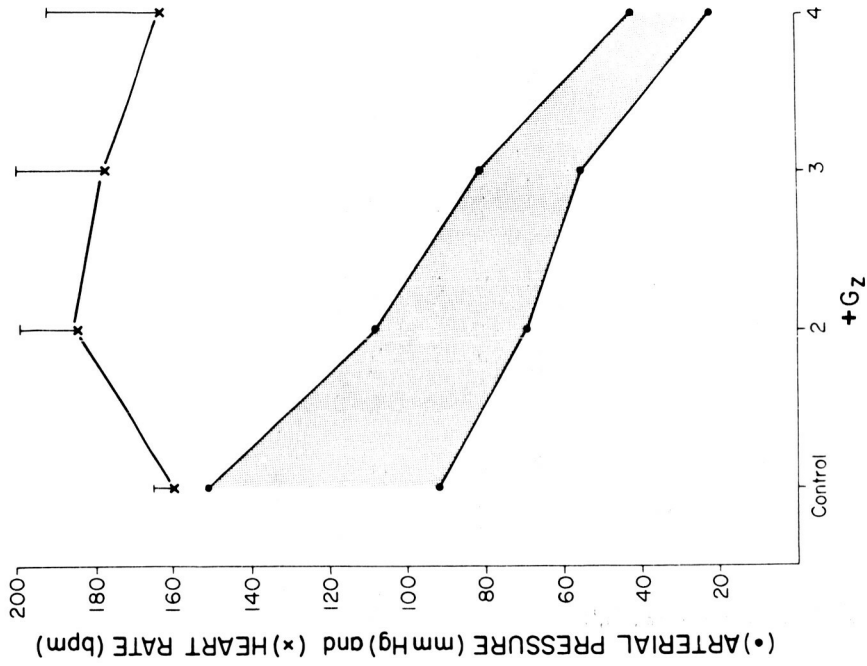


Figure 14.— Average change in heart rate and arterial systolic and diastolic pressure at various levels of +G<sub>z</sub> acceleration. Bars through the points represent one SEM.

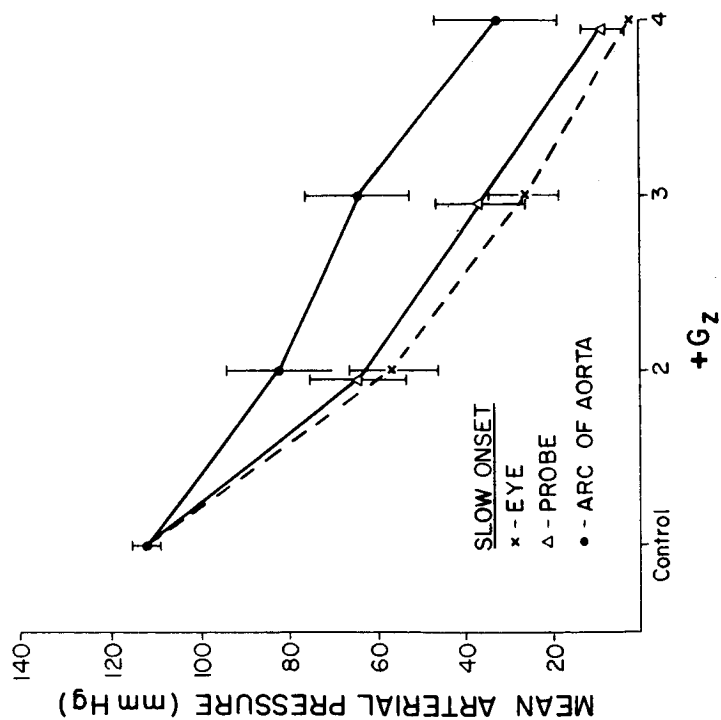


Figure 15.— Average mean arterial pressure at three different locations in the circulation with various  $+G_z$  acceleration levels. Bars through the points represent one SEM.

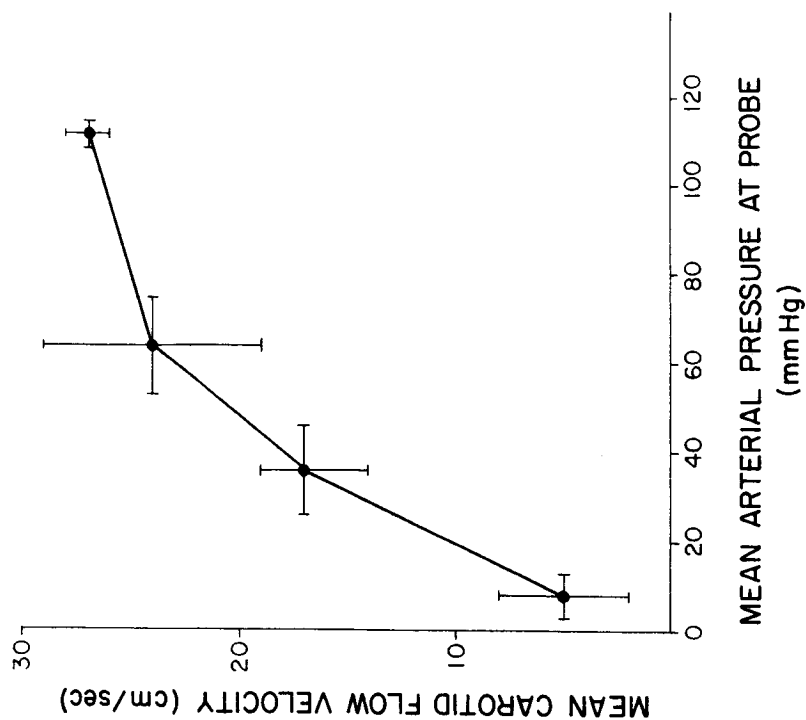


Figure 16.— Mean carotid flow velocity and mean arterial pressure at the site of implantation of the flow probe. The points were taken at various pressure levels during  $+G_z$  acceleration. Bars through points represent one SEM.

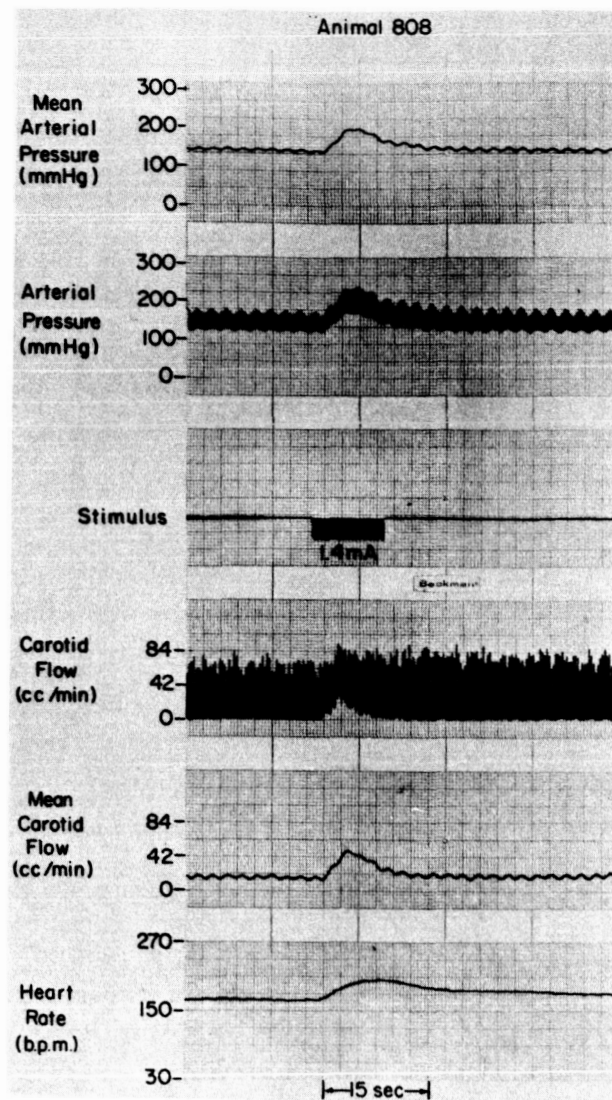


Figure 17.— Typical response to cerebellar stimulation in the monkey. Stimulation was accomplished in the fastigial nucleus.

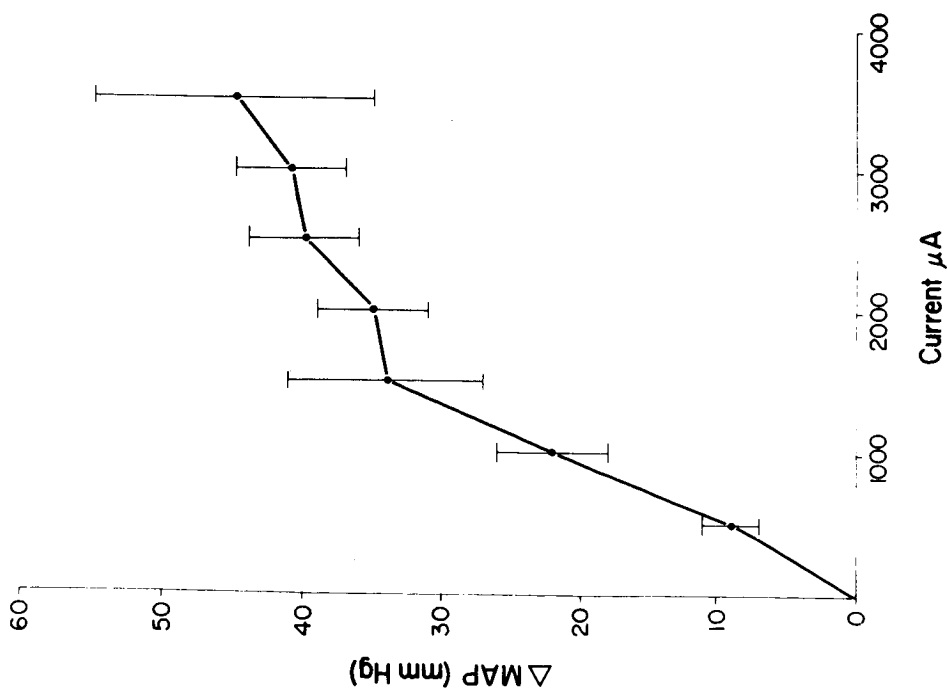


Figure 18.— Mean arterial pressure versus current of cerebellar stimulation. The bars through the points represent one SEM.

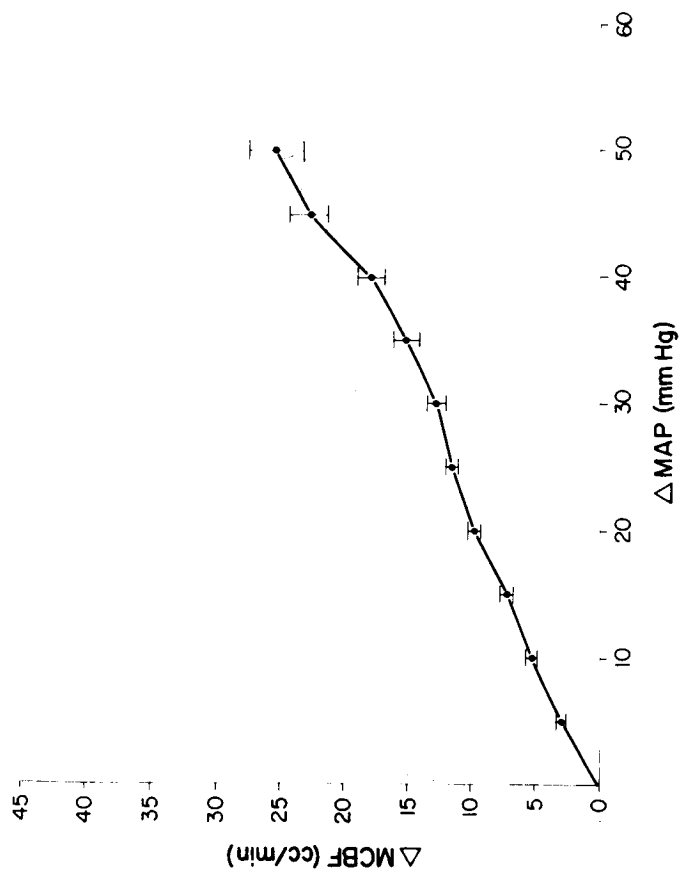


Figure 19.— The change in mean carotid blood flow versus the change in mean arterial pressure during cerebellar stimulation. Bars through the points represent one SEM.

## SOME EFFECTS OF ACCELERATION IN MAN AND CHIMPANZEES\*

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This paper concerns the effects on biomedical systems, especially in intact humans, of changes in the force environment, particularly such as those encountered in long-duration space flights. Some simple basic considerations are in order to lead into my discussion. Changes in the force environment can be produced by changes in either the magnitude or direction of the gravitational field as well as by changes in the direction or magnitude of velocity. Consequently, I prefer to precede the term "force environment" by the two adjectives "gravitational" and "inertial"; that is, we are interested in effects of changes in the gravitational-inertial force environment.

It should be remembered that, unlike other environmental quantities, such as temperature or barometric pressure, which are scalar quantities that vary only in magnitude and rate of change, the force environment is a vector quantity; that is, it varies, not only in magnitude and rate of change, but also in direction in relation to the biomedical system under study.

A more appropriate title for my remarks would be: "Some effects of changes in the gravitational-inertial force environment on the cardiovascular and pulmonary systems of large primates." Aside from some studies of the effect of changes in body position (i.e., in the direction of the force environment), the onset of serious detailed studies of the effect of changes in the force environment on man were ushered in by the blackout phenomena experienced by pilots during aerobatic maneuvers just prior to and during World War II. This was a tactically important factor in aerial dog fights during this period and, hence, gave impetus to the building of human centrifuges in both the Axis and Allied countries and the carrying out of studies on these machines during this period.

Since I don't recognize anyone in this audience who either was old enough at that time or had both the interest and the opportunity to be involved in these early force-environment studies which were carried out over 30 years ago and since prior speakers have painted some historical background for their remarks, I will take the liberty to sketch some of the early results of studies of changes in the force environment on the cardiopulmonary system, particularly those performed in the Department of Physiology and Biophysics of the Mayo Foundation in Rochester, Minnesota.

Figure 1 is a picture taken in 1942 of the human centrifuge at the Mayo Foundation, Rochester, Minnesota. This is the oldest modern human centrifuge in the nation. By modern human centrifuge, I mean one which is large in relation to the size of the subject and which has the power

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capabilities to start and stop rapidly so that it can simulate the rapid changes in centripetal acceleration encountered in aerobatic maneuvers in aircraft.

Figure 2 is a picture of the device used for the first physiologic experiments carried out on this centrifuge. At that time, most of the authorities on the effects of acceleration, such as Poppen and Franks in Canada, were convinced that the major deleterious effects of positive acceleration were primarily due to the fact that the increased weight of the blood caused by acceleration prevented or reduced venous return to the heart from the dependent regions of the body (refs. 1-3). To study this factor, we built a steel container or "bathtub" which could be fitted into the cockpit of our centrifuge. The bathtub was filled with water to various levels on the thorax of the subject and the protective effects of this nearly theoretically perfect support to venous return against the pathophysiologic effects of acceleration studied. Much to our disappointment, this proved to be relatively an ineffectual means of preventing the loss of vision and/or consciousness produced by positive acceleration (ref. 4).

Figure 3 is a picture of a human primate subject in the cockpit of the Mayo human centrifuge. It has been our experience that, for studies of the effects on aircraft occupants of exposure to positive accelerations of several or more seconds duration, humans are by far the experimental subject of preference. It is perhaps not an exaggeration to say that the many studies which were done on anesthetized dogs and anesthetized primates during and after World War II contributed very little to understanding the effects of positive acceleration on unanesthetized human beings.

Simultaneous recordings of 12 physiologic variables shown in figure 4 give some idea of how these human centrifuge subjects were instrumented for hardwired telemetry from the human centrifuge to an adjacent recording room. Such continuous recordings of multiple variables on normal, awake humans were unique back in the 1940's (ref. 5). The simultaneous recordings of arterial pressure, recorded directly from the two radial arteries at the wrist, one supported at heart level and the other at head level during exposure to 4.5 g for a period of 15 sec, illustrate that, although arterial pressure at head level decreased to zero, there was practically no change in arterial pressure at heart level during the initial 5 sec of the exposure. A remarkable increase in arterial pressure at heart level, up to 200 mm Hg systolic, then occurred, in spite of the fact that the exposure to acceleration continued.

These findings highlight the fact that a decrease in venous return is not the major factor which limits a normal individual's tolerance to positive acceleration. The actual limiting factor, as illustrated diagrammatically in figure 5, is the normal level of arterial pressure at heart level which, in the face of, for example, the fivefold increase in the weight of the blood which pertains during an exposure to 5 g, is insufficient to provide an arterial pressure at head level sufficient to maintain circulation to the retina and brain. The left panel of this figure illustrates the usual position of an aircraft pilot and the middle panel is a hydrostatic diagram of his cardiovascular system at 1 g. In this normal force environment, about 24 mm Hg is required to lift the blood up to his head. An exposure to 5 g increases the hydrostatic distance between his heart and brain five times. Consequently, although arterial pressure is essentially normal at 120 mm Hg systolic at heart level, this pressure is insufficient to support a column of blood up to head level. Blood pressure, therefore, is reduced to zero at brain level at the onset of such an exposure and symptoms of cerebral and retinal ischemia occur.

Figure 6 shows one of the partial solutions to this problem, used during and after World War II. This was the development (in collaboration with Mr. David Clark of the David Clark Co.) of a very simple air-bladder system which could be incorporated into various types of close-fitting garments and inflated with ambient air, via an associated pressure control valve, to a single, high pressure (about 50 mm Hg/g) during exposure to positive acceleration. This applied a high pressure to the legs and particularly to the abdomen, and, essentially, pressure injects the central circulation simultaneously with an increase in peripheral resistance, thus producing a significant and sustained increase in arterial pressure (refs. 6 and 7).

Figure 7 shows such a suit and the g-activated and g-compensated valve which provided automatic control of the onset and degree of inflation (i.e., pressure) of the suit air-bladder system during exposure to acceleration. This simple suit and valve, designated "model 21" in the Mayo human centrifuge and laboratory, is actually the prototype of the antiblackout suits and valves which are still used today.

Figure 8 shows the effects of suit inflation on arterial pressure at heart and head level at 1 g and during an exposure to 6 g. During a control exposure to 4.5 g, this subject's blood pressure dropped to 0 at head level and a complete loss of vision, that is, blackout occurred. Inflation of the bladder system to about 250 mm Hg when the subject was at 1 g (center panel) produced a sudden and sustained increase in arterial pressure at heart and head levels. Inflation of the suit to a similar pressure during an exposure to 6 g increased arterial pressure to an even greater degree, 250-mm systolic pressure at heart level. This increase in pressure at heart level was sufficient to lift the blood up to and maintain a sufficient pressure at head level so that the complete loss of vision which had occurred during the control exposure to 4.6 g was prevented at this higher level of acceleration. In other words, the artificially produced hypertension of 250 mm Hg at heart level was sufficient to provide the arterial pressure at head level required to maintain circulation to the brain and retina during an exposure to a positive acceleration of 5.5 g.

The foregoing, since it occurred back in the 1940's, is ancient history in relation to our modern day space age. Figure 9, which is the g-profile of the launch phase of John Glenn's first United States manned orbital space flight, illustrates a more recent concern. During the blast off and booster phase of this launch, Glenn was exposed to a transverse acceleration of over 6 g for two periods, one for 35 sec and one for 54 sec. Because of these high levels of acceleration, the astronauts, as you all know, were supported in the "mercury-couch" position so that the reactive force was transverse to the long axis of the body in  $+G_x$  or "eye balls in" direction. At this time, transverse accelerations in the 5- to 6- $G_x$  level were considered to be relatively innocuous. However, more detailed centrifuge studies of the effects of these levels of  $+G_x$  acceleration revealed that transverse acceleration of this magnitude was not quite as innocuous as had been presumed.

The studies of the effects of long-duration (1 to 5 min) exposures to positive and transverse accelerations carried out on the Mayo centrifuge have been supported during the last approximately 15 years by research grants from the United States Air Force and the National Aeronautics and Space Administration (refs. 8-50). Figure 10 shows a typical subject reclining in the mercury couch in the cockpit of the centrifuge and instrumented for simultaneous continuous photokymographic recordings, one of which is shown in figure 11. The changes in aortic pressure and respiration are small, but the continuous recordings of the oxygen saturation of blood being sampled continuously from the radial artery via a cuvette oximeter and also another record of arterial oxygen saturation by an absolute reading ear oximeter (refs. 51 and 52) show dramatic decreases in arterial oxygen

saturation during this exposure to 5.5 g for 3 min. This level of acceleration is approximately what the astronauts experienced during the launch phase of space flights at that time. The averages and the ranges of these effects on the arterial oxygen saturation in four normal male subjects are shown in figure 12.

Exposure to transverse accelerations at these levels also has a rather dramatic effect on right atrial pressure at heart level, as illustrated in figure 13, which is a plot of atrial pressures in five normal human subjects during exposures to 2, 3.5, and 5  $G_x$ . These very large increases in right atrial pressure were a source of considerable worry to the Air Force at that time, since the possibility had not been excluded that they might be the result of some type of cardiac failure. However, measurements of esophageal pressures in humans and of pericardial pressures in dogs during similar exposures demonstrated that the increases in these intrathoracic pressures were closely similar to the simultaneous increases in right atrial pressure. Consequently, there was little or no change in transmural atrial pressure, and the increased atrial pressures were the result of increases in intrathoracic pressures rather than a change in filling pressure to the heart.

Another effect of this type of acceleration, of more serious impact, was revealed by chest roentgenograms obtained from normal subjects at maximum inspiration before and after an exposure to 5 g for 3 min (fig. 14). The elevation of the diaphragm and the increases in roentgen opacity in the basal regions of the lungs 1 min after the exposure are evident. Our clinical radiology colleagues interpret these changes as indicative of atelectasis, that is, collapse of the alveoli in the dependent, dorsal aspects of the lungs.

A diagram of the probable physical explanation of these effects is shown in figure 15, the middle panel of which is a diagram of a human chest and the probable intrathoracic pressures at 1 g. The circles represent the alveoli connected by springs to indicate their inherent elasticity which would cause their collapse except for the negative intrapleural pressure surrounding the lungs. This diagram is based on the assumption that the thoracic contents behave as a hydrostatic system. The average specific gravity of the thoracic contents has been assumed to be 0.5 and pleural pressure  $-7$ , venous pressure 10, and pulmonary arterial pressure 20 cm  $H_2O$ , respectively, at midchest level. Due to the weight of the blood and the thoracic contents, the arterial and venous pressures, and hence pulmonary capillary pressures, would be expected to attain maximum levels in dependent regions of the lungs and be minimum at the superior margin of the lungs. Similarly, pleural pressures would be least negative in the dependent, and most negative in the superior, regions of the chest. During an exposure to 5 g (right panel), the weight of the thoracic contents is increased five-fold so that, on the basis of simple hydrostatic considerations, if venous and arterial pressures are unchanged at midchest levels, these pressures would be increased to 60 and 70 cm  $H_2O$ , respectively, at the most dependent regions of the lungs, and rapid development of pulmonary edema in the dependent regions of the thorax would be expected. Also, on the basis of these assumptions, it would be expected that pleural pressure would increase to a positive value of about 18 cm  $H_2O$  in dependent regions and decrease to proportionally a much higher negative value in the ventral, superior portions of the thorax. Consequently, the alveoli would be severely overdistended in the superior portions of the chest concomitantly with their collapse in the dependent regions.

This diagram provides the basis for logical explanations for both the roentgenographic evidence of pulmonary atelectasis and the demonstration on the Mayo and other centrifuges of severe degrees of arterial hypoxemia presumably due to pulmonary arterial venous shunting in the dependent regions of the thorax of normal subjects during exposures to high levels of transverse acceleration.



Furthermore, the rather frightening incidents of disruption of pulmonary parenchyma with development of acute mediastinal emphysema, such as has occurred during exposure to high levels of acceleration in our and other laboratories (refs. 7, 13, and 53), are not surprising since transalveolar pressures of about 40 cm H<sub>2</sub>O are believed to be sufficient to rupture alveoli in some subjects.

In relation to the use of experimental animals as surrogates for human subjects in acceleration studies, it should be remembered that the effects of changes in the force environment on the lungs and vascular system are directly related to the vertical heights spanned by these systems. The fact that mice can survive exposures to accelerations as high as 400 g is undoubtedly related to the very small dimensions of the mouse thorax. On this basis, small primates such as the squirrel monkey cannot be considered as a satisfactory surrogate for humans in space-flight experiments.

The findings of arterial hypoxemia and, particularly, the occurrence of acute mediastinal emphysema in a normal subject during an exposure to transverse acceleration (ref. 13) were the impetus to study the effects of changes in the direction and magnitude of the gravitational-inertial force environment on intrathoracic pressure relationships, particularly pleural and pericardial pressure. Since insertion of catheters into the potential pleural and pericardial spaces of normal human subjects is not considered to be a safe procedure, we resorted to the use of anesthetized experimental animals. The first animal used was the dog, since the maximum dorsal-ventral dimensions of the dog lung is similar to that of man. Figure 16 illustrates the assembly used for studying intrapleural pressures by saline-filled catheters inserted percutaneously into the pleural space and manipulated to various vertical heights in the thorax by an airtight technique. Figure 17 is a picture of such an animal supported within the X-ray system in the cockpit of the human centrifuge by means of a radiolucent half-body plastic cast.

Lateral thoracic roentgenograms of the dog supported in the prone position at 1 and  $-6.4 G_x$  (fig. 18) show the various catheters in place for recording dorsal and ventral, esophageal, aortic, right atrial, pulmonary artery, right ventricular, pericardial and pulmonary venous (left atrial) pressures. The thistle-tube systems on either side of the thorax are filled with saline to midchest level and connected in parallel. This hydrostatic system can be connected simultaneously by means of a remotely activated, power driven stopcock assembly to all of the strain-gauge manometers for automatic recording of the zero-reference (midchest) level for each of the catheter manometer systems. This system, coupled with biplane thoracic X-rays, is a vitally important capability for accurate recording of multiple vascular and intrathoracic pressures particularly during changes in direction and/or magnitude of the force environment. The displacement of the animal's diaphragm and the increase in radiolucency of the superior (dorsal) lung fields during the exposure to  $-6.4 G_x$  are evident.

Figure 19 is a photokymographic recording of multiple pressures in such an animal. The changes in arterial oxygen saturation and systemic arterial, atrial, and esophageal pressures were similar to those recorded in human subjects, suggesting that, for this type of experiment in which cardiovascular reflexes do not play an important role, the dog may be a reasonably satisfactory surrogate for man. The deleterious effects of acceleration on the lungs are believed to be the result of hydrostatic physical phenomena which are not affected to a practically significant degree by cardiovascular reflexes.

Figure 20 shows the average effects on seven dogs of forward accelerations of 6 to  $7 +G_x$  on the topographic relationships of the heart and lungs determined from biplane thoracic

roentgenograms. At 1 g in the supine position, the heart is located superiorly (ventrally) in the thorax with its ventral margin juxtaposed to the parietal pleural surface of the ventral chest wall. During the exposures to 6 to 7  $+G_x$ , because the specific gravity of the heart and its blood contents is much greater than the surrounding air-filled lungs, the heart is centrifuged (displaced) towards the dependent dorsal portions of the chest. This rather dramatic dependent displacement of the high specific gravity heart must be associated with over distention of the lungs in the superior, ventral portion of the lungs with their concomitant compression in the dependent portion of the thorax. These anatomic displacements supported the subsequently confirmed prediction that high vertical pleural pressure gradients must be produced under these circumstances with highly negative values superiorly and a concomitant increase inferiorly to possibly positive values with consequent atelectasis in the dependent regions of the thorax (ref. 13).

The plot of superior and dependent end-inspiratory and end-expiratory pleural pressures and of esophageal pressures in a dog before, during, and after an exposure to 6 g (fig. 21) confirms these predictions. The changes in dorsal (dependent) pleural pressure and esophageal pressures, which were recorded at similar vertical heights in the thorax, were closely similar, increasing to positive values of about 30 cm  $H_2O$  at end-expiration and remaining above, or only slightly below, zero at end-inspiration. It is of interest that, even during inspiration, pleural pressure at this dependent level in the chest remained mostly positive, indicating there would be no alveolar ventilation in this region of the lungs during inspiration, so that a significant dependent pulmonary arteriovenous shunt would be expected. This would explain the striking decrease in arterial oxygen saturation which occurs.

That this is indeed the case is illustrated in figure 22, which is a plot of the oxygen saturation values of blood being withdrawn continuously and simultaneously from the right and left pulmonary veins, the aorta, and pulmonary artery of a dog lying on its left side before, during, and after an exposure to  $-7 G_y$ . The pulmonary venous blood draining the superiorly positioned right lung remained fully saturated throughout the exposure, while the oxygen saturation of blood which had traversed the dependent (left) lung decreased during the exposure to values identical to the pulmonary arterial blood entering the lungs, indicating that there was no oxygenation of the blood traversing the dependent portion of the lung during this period. This is a convincing demonstration that the arterial hypoxemia, which develops during exposures to an increased gravitational inertial force environment, is caused by dependent pulmonary arterial-venous shunting, which, in turn, is presumably caused by atelectasis in the dependent portions of the lung, which condition is caused by the increased weight of the superposed thoracic contents. Since the deleterious effects of changes in the force environment on the lungs are due to the very large difference between the specific gravity of the gas-filled alveoli and other intrathoracic structures, particularly the blood and heart, replacement of alveolar gas with a liquid with a specific gravity similar to that of blood and tissue should protect against these effects.

Figures 23 and 24 illustrate the equipment used for study of the effects of breathing liquid fluorocarbon on force-environment dependent regional differences in intrathoracic pressures, blood flow, and oxygenation. The protection afforded by breathing liquid fluorocarbon against the arterial hypoxemia produced by an exposure to an acceleration of  $+6 G_y$  (ref. 41) is illustrated in figure 25.

The foregoing has been a brief resume of the results of studies of the effects of transverse acceleration on anesthetized dogs carried out on the Mayo centrifuge. Although the results of

arterial oxygen saturation studies in man and anesthetized dogs were similar, because the dog thorax is much different in both shape and dimensions from that of man, transfer of results obtained in dogs to humans is not warranted. The striking difference in the configuration and dimensions of typical cross sections of dog and human thoraces is illustrated in figure 26. The fact that the anterior-posterior dimension of the dog thorax is similar to that of adult man is probably responsible for the fact that the degrees of arterial hypoxemia caused by exposure to the same levels of forward and backward acceleration ( $\pm G_x$ ) are similar in the two species.

In choosing an experimental animal as a surrogate for man, particularly for studies of the effects of changes in the gravitational-inertial force environment associated with space flight, it is of considerable importance that the physical dimensions of the animal, particularly of the thorax, be similar to that of man. This is because the force-environment dependent, potentially dangerous, range of transalveolar pressures from the superior to dependent margin of the lungs is proportional to the anatomical extent of the thoracic cavity parallel to the resultant vector of the gravitational-inertial force environment (fig. 15).

The importance of the physical dimensions of the thorax as a determinant of tolerance to high levels of acceleration is exemplified by comparing lethal levels of acceleration for mice and chimpanzees. Exposures to acceleration of 30 g are lethal to most chimpanzees due to rupture of the pulmonary parenchyma (ref. 53), while mice may survive exposures to 400 g. Quite certainly, this dramatic difference is due to the fact that the differential pressures generated across the 1-cm transverse diameter of the mouse thorax during an exposure to 400 g would be expected to be similar to the range of hydrostatic pressure across the 20-cm-thick thorax of a chimpanzee during an exposure to 20 g.

Primates, whose thoracic dimensions are much smaller than those of humans, such as monkeys, particularly squirrel monkeys, are, from this point of view, poor surrogates for man. Because of these considerations, we have studied (with the support of the Air Force and NASA) the effects of transverse acceleration on chimpanzees for a number of years (ref. 33).

Figure 27, which is an anterior-posterior thoracic roentgenogram of a chimpanzee, illustrates the similarity of the shape and dimensions of the chest of a chimpanzee to that of man. Multiple catheters were introduced by percutaneous needle punctures and manipulated so that their tips were located in the pulmonary artery, aorta, left atrium by transeptal puncture, right ventricle, left and right pleural spaces, and the esophagus. Since these multiple catheters were inserted percutaneously without resort to surgical exposure of the peripheral vessels, these vessels remained functional so the same animals could be studied on multiple occasions, as many as four times, using the same vessels for introduction of the multiple catheters by the percutaneous needle introduction technique.

Figure 28 is a picture of this chimpanzee positioned in the cockpit of the Mayo human centrifuge. The multiple catheters are connected to strain-gauge manometers and/or cuvette oximeters for continuous recording of circulatory and pleural pressures from multiple sites in the thorax and blood oxygen saturation from the pulmonary and femoral arteries.

Thoracic roentgenograms of such a chimpanzee before (left panel) and during (right panel) an exposure to  $+5.8 G_y$  are shown in figure 29. The positions of the tips of the multiple recording catheters are indicated by appropriate letters. The dramatic increase in volume and radiolucency of

the superior (right) lung, the displacement of the heart and other mediastinal structures into the lower chest, the caudad displacement of the right (upper) dome of the diaphragm, cephalad displacement of the left dome and concomitant increased opacity of the lower lung are evident and similar to the changes produced in the dog.

The thoracic roentgenograms in figure 30 illustrate that, just as in humans, on some occasions, the atelectasis of the dependent regions of the lungs produced by acceleration in chimpanzees does not clear up immediately after return to 1 g. These roentgenograms were taken after the chimp had been on his left side for 1.5 hr (right panel), 3 hr later, after exposures to  $+G_y$  acceleration, and 2 hr still later, 15 min after return to the supine position. Persistent atelectasis of the left lung, which was dependent during the repeated exposures to acceleration, is evident.

The chimpanzees used for these studies were often kept under anesthesia for as long as 24 hr, from about 7:00 or 8:00 in the morning at the onset of the procedure until its completion of the experimental protocol the next morning. Out of the approximately 20 such studies we have carried out, as many as four on single chimpanzees, there have been two chimpanzees lost, none of them during the experiment. One of them was euthanized several weeks after an experiment due to a severe infection in a large unresolved hematoma which developed at an arterial puncture site in the femoral artery following the experiment. A second animal was lost due to a large unrecognized retroperitoneal hemorrhage, which occurred during the experiment through the posterior wall of the femoral vein, perforated inadvertently when the transeptal left atrial puncture needle was inserted at the beginning of the experiment.

The type of photokymographic recordings of multiple physiologic variables obtained in these chimpanzees is illustrated in figure 31, and the results of the systemic arterial and mixed systemic venous blood oxygen saturation studies measured from these recordings are shown in figure 32. The changes in arterial oxygen saturation are similar to those observed in humans and dogs in both the prone and supine positions. The same type of results (fig. 33) was obtained when the chimpanzees were breathing 100 percent oxygen. The decreases in arterial blood oxygen saturation in this circumstance are indicative of a true anatomic pulmonary arterial venous shunt, which ranged from 20 percent to 40 percent of total pulmonary blood flow during exposures to transverse accelerations of about  $7.4 G_x$ .

The intrapleural pressures in dorsal and ventral regions of the thorax and esophagus during exposures of 2, 4, and  $6 G_x$ , when the vertical heights of these recording sites in the thorax of the chimpanzee were reversed by changing the body position from prone to supine, are shown in figure 34. Just as had been observed previously in the dog, pleural pressures in whichever sites were superior in the thorax decreased to highly negative values, while, concomitantly, the liquid pleural pressure at dependent sites increased to positive values.

The positive values, as high as 60 cm  $H_2O$ , in dependent regions of the chest would certainly be expected to be associated with collapse and nonventilation of the lung in these regions of the thorax. Likewise the highly negative values, as high as  $-60$  cm  $H_2O$ , in the superior portions of the chest and the associated very high transalveolar pressures would be expected to be capable of producing actual anatomic damage, that is, disruption of the anatomically fragile alveoli (refs. 7, 13, and 53).

The average and range of aortic and pulmonary arterial pressures in these animals in the 1-g control situation plus the changes in these pressures recorded during exposures to transverse accelerations of about 3 and 6  $G_y$  are given in figure 35. The large range in the central pulmonary arterial pressure values suggest that the pulmonary vascular resistance of these animals is quite labile. Quite high pulmonary artery pressures of over 40 cm  $H_2O$  were quite frequently recorded in these chimpanzees, particularly during some degree of hypoxemia associated with depressed pulmonary ventilation caused by anesthesia and very long periods in the same body position. Pulmonary artery pressures at midchest level were nearly always increased during exposures to transverse accelerations of more than 5 g and not infrequently to very high levels of more than 100 cm  $H_2O$ . The control levels of pulmonary pressure were reduced significantly when breathing 100 percent oxygen.

The evidence of severe distortions of the pulmonary parenchyma and large pulmonary arterial-venous shunts during exposures to increases in the force environment suggests that large changes in the spatial distribution of pulmonary blood flow may occur under these circumstances. Our belief that such changes do occur, and the hope that studies of these changes might increase our understanding of the mechanisms which control the regional distribution of pulmonary blood flow in the normal 1-g force environment of planet Earth was the impetus for our studies of the regional distribution of pulmonary blood flow associated with the changes in intrathoracic pressure relationships, parenchymal strains, blood oxygen saturation, and ventilation distribution produced by changes in the direction and magnitude of the gravitational-inertial force environment (refs. 30–42).

Because of the nature of the techniques used and exposure to ionizing radiation, such studies are contraindicated in normal human subjects. Because of the close similarity between the shape and dimensions of the thoraces of chimpanzees and humans, these animals are particularly well suited for these investigations.

Similar studies were carried out in dogs prior to the use of these techniques in chimpanzees (refs. 35–52).<sup>1</sup> This technique involves injection of radioactive microspheres of about 35  $\mu m$  in diameter into the right ventricle of these animals. The microspheres mix quite uniformly in the blood during traversal of the pulmonary valve and embolize the microvasculature of the lung in direct proportion to the blood flow through these vessels. After removal from the centrifuge cockpit, the chimpanzees were placed in plastic molded half-body casts to maintain constant body positions while a computer-controlled scintiscanning system was used to obtain a two-dimensional map of the amount of radiation emanating from the dorsal and then the ventral surfaces of the thoraces of these animals (fig. 36). By using four different batches of microspheres tagged with isotopes of different energies which could be differentiated by pulse-height analysis, it is possible to obtain four determinations of the spatial distribution of pulmonary blood flow under four different conditions.

Figure 37 shows computer-generated simulated three-dimensional plots of the distribution of pulmonary blood flow in an anesthetized chimpanzee lying on his left side. The smaller blood flow to the superior right lung and the tendency for this flow to be displaced towards the dependent (medial) border of the superior lung is evident as is the maximal region of flow towards the midline of the dependent (left) lung.

<sup>1</sup> Also in "Effects of an Increased Force Environment on Spatial Distribution of Pulmonary Blood Flow in Dogs," by J. F. Greenleaf, E. L. Ritman, D. J. Sass, and E. H. Wood. Submitted to J. Appl. Physiol.

The effects of an exposure to an acceleration of  $+5.8 G_y$  on spatial distribution of pulmonary blood flow in a chimpanzee lying on his left side are shown in figure 38. The preponderance of blood flow to the dependent lung is exaggerated during exposure to 5.8 g, as one might expect. However, the increase is chiefly in the upper midregion of this lung rather than to the more dependent regions as might be expected to occur on a simple hydrostatic basis. The calculated physiologic pulmonary arterial-venous shunts based on the oxygen saturation of systemic and pulmonary arterial blood were 12 percent and 63 percent at 1 and  $5.8 G_y$ , respectively.

External scanning studies encompassing the full cephalocaudad extent of (prior to the direct scintiscanning of every coplanar 1-cm-thick cross section in) the entire lungs was carried out in the lungs of the chimpanzee that died shortly after the experiment due to an unrecognized retroperitoneal hemorrhage. Figure 39 is a three-dimensional computer plot of the dimensions and shape of the excised lungs of this chimpanzee. Figure 40 shows the distribution of the energy specific radiation in a cross section of the lungs, midway between the apex and the base of the lungs, emanating from microspheres injected into the right ventricle at 1 and  $5.8 G_y$ , respectively. The higher level of blood flow to the dependent left lung at 1 g is evident, as is the exaggeration of this effect at 5.8 g, particularly the displacement of the flow in the upper lung towards its dependent medial margin.

The same types of data for alternate 1-cm-thick cross sections extending over the full cephalad-to-caudad dimensions of the lungs for the specific microspheres injected at 1 and 5.8 g are shown in figures 41 and 42, respectively. The distribution of blood flow along the apical to basal extents of the two lungs is relatively uniform at  $1 G_y$ , with a greater fraction of the blood traversing the lower lung in this situation.

During the exposure to  $5.8 G_y$ , the displacement of blood flow in the upper lung towards its medial margin and the maintenance of blood flow to the superior medial region of the dependent lung are evident over their full cephalo-to-caudad extents. Thus, pulmonary blood flow in the midregions of the thorax is maintained or increased in the same regions at which transalveolar pressures, ventilation, pulmonary arterial and venous pressures, and blood-gas exchanges are minimally affected by changes in the force environment.

Figure 43 is a picture of some of the technical and professional personnel who were involved in these centrifuge experiments in 1968 and indicates that the studies presented herein were made possible by a large team of dedicated people whose efforts, along with others not shown, have been expended over a time period of more than two decades to make these studies possible (refs. 2–52).

The last series of figures provide a glance into the future in relation to heretofore impossible types of studies of changes in cardiac, pulmonary, and circulatory dynamics caused by changes in the force environment such as encountered in space flight and existence in extraterrestrial environments. These studies will be made possible by a new and revolutionary technique (refs. 54–57) whose potential for heretofore impossible studies of the relationships of the dynamic changes in the spatial geometry of the heart, lungs, and circulation to the function of these organ systems is just beginning to be recognized (refs. 58–62). This technique, known as axial tomography or three-dimensional reconstruction, has provided amazingly accurate anatomical reconstruction of the brain of patients with suspected cerebral abnormalities (refs. 54–57) and, more recently, of moving organ systems such as the heart, lungs, and circulation of intact animals and man (refs. 58–62).

Although the development and applications of these techniques are still in their infancy, consideration of their potential in relation to space flight studies is not premature, since the very rapid progress in miniaturization of computers, X-ray detectors and transducers will make it possible to apply these techniques in the quite large orbiting laboratories currently in the advanced development stage for implementation in the near future. Figure 44 provides an intuitive impression of the basis for cross-sectional reconstruction techniques. Multiple cross-sectional density profiles of a structure such as the heart contain considerable information concerning the shape and dimensions of the cardiac chambers and the internal structure of this organ. The very high speed and volume of data handling and levels of computing power currently available with state-of-the-art electronic data processing and computing technologies have reduced the problem of dynamic (60/sec) spatial reconstructions of the heart, lungs, and circulation from this type of multiplanar projection data into the realm of practicality. These techniques are ideal for studies of, for example, the changes in volume and function of heart, lungs, and circulation during variable duration exposures to zero g.

Figure 45 is a diagram of a new generation system which will be utilized to generate the data required to obtain stop-action (0.01-sec exposures) spatial reconstructions of, for example, the heart, lungs, and intrathoracic circulation at rates up to 60/sec during several heart beats or respiratory cycles, as desired. This dynamic spatial reconstruction system (DSR) will consist of a radiolucent animal or patient couch mounted in the center of a semicircular array of 28 X-ray sources and an opposing array of 28 fluorescent image intensified video systems. This X-ray source-image transducer array is operated in a computer-controlled, sequentially pulsed mode so that the 28 multiplanar exposures required to obtain the data necessary for a single spatial reconstruction can be obtained in a short enough exposure time (0.01 sec) to obtain stop-action spatial reconstructions of the heart and circulation and at a repetition rate (60/sec) required to resolve most practically important phasic events within individual cardiac and/or respiratory cycles.

Figure 46 shows our first attempt to reconstruct a cross section of the thorax of an intact dog using a Mark 1 prototype of a single unit of this 28-unit system, the SSDSR (refs. 50 and 59). The external, parietal, and pleural surfaces of the lungs and the epicardial surfaces of the heart can be visualized noninvasively, that is, without injections of contrast medium.

Figure 47 shows dynamic reconstructions of cross sections of the thorax at multiple cephalad-caudad levels of the chest during the respiratory cycle in an intact dog. These thoracic cross sections can be reconstructed from each of the approximately 200 video lines that cross the projection images of the chest and for any 0.01-sec duration phase in the respiratory cycle desired. These types of dynamic spatial information concerning anatomical shapes, dimensions, volumes, and simultaneous pressure and flow data will allow studies of, for example, dynamic changes in spatial distribution of pulmonary ventilation and blood flow which have been impossible heretofore. These techniques will open up a whole new avenue of physiologic studies, both in intact animals and human surrogates, such as chimpanzees, as well as in clinical diagnostic environments in patients with suspected cardiopulmonary or circulatory disabilities.

Figure 48 demonstrates that these cross-sectional reconstruction techniques can be used with ultrasound radiation as well as with X- and  $\gamma$ -rays. This is a cross-sectional reconstruction of the heart from multiple projection profiles of the transmission velocities of ultrasound through a canine heart. The shape and dimensions of the epicardial and endocardial surfaces of left and right ventricles are well visualized, along with some indication of regional variations in the density of the myocardium (refs. 61 and 62).

These very exciting, new, dynamic computer-based quantitative imaging techniques are opening up new horizons for the study of moving organ systems of man and animals, both in everyday life on planet Earth as well as the ever-broadening expanse of manned exploration of space.

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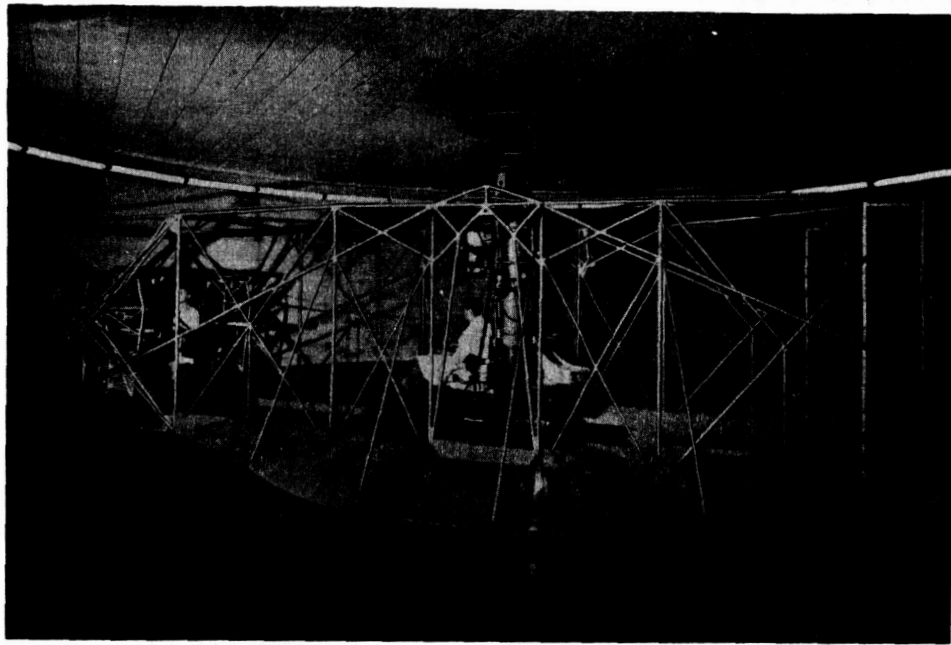


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**Figure 1.—** Human centrifuge facility at the Mayo Clinic. The observer controls the time of starting and stopping of the centrifuge and tests the subject's vision throughout the period of exposure by activating lights mounted on the subject's instrument panel in the cockpit at his fixation point (central vision) and  $23^{\circ}$  from his fixation point (peripheral vision). The subject's response times to these light signals and the alterations in other physiological parameters are transmitted electrically through a commutator system mounted on the center shaft of the centrifuge; they are recorded photokymographically in an adjacent room. See figure 4 for an example of physiological recordings obtained with this assembly.



Figure 2.— Steel container designed for study of the effects of immersion in water to various levels on the tolerance of normal subjects to the effects of headward acceleration. The container was placed in the centrifuge cockpit (fig. 1) and the effects of acceleration on the subject seated within it were compared for when the tank contained no water and for when it was filled to various levels on the body.



Figure 3.— Subject on the human centrifuge. (a) At 1 g prior to centrifugation. (b) At 5 g during rotation of centrifuge. Note that the soft tissues of the face and neck are being drawn downward, producing the appearance of increased age. The mouthpiece contains a thermocouple for recording respirations (as temperature variations) in the airway. The two oximeter-type eartypes supported on the headband are used for recording the blood content of the ear (ear opacity) and the change in opacity of the ear produced by each heartbeat (ear opacity pulse).

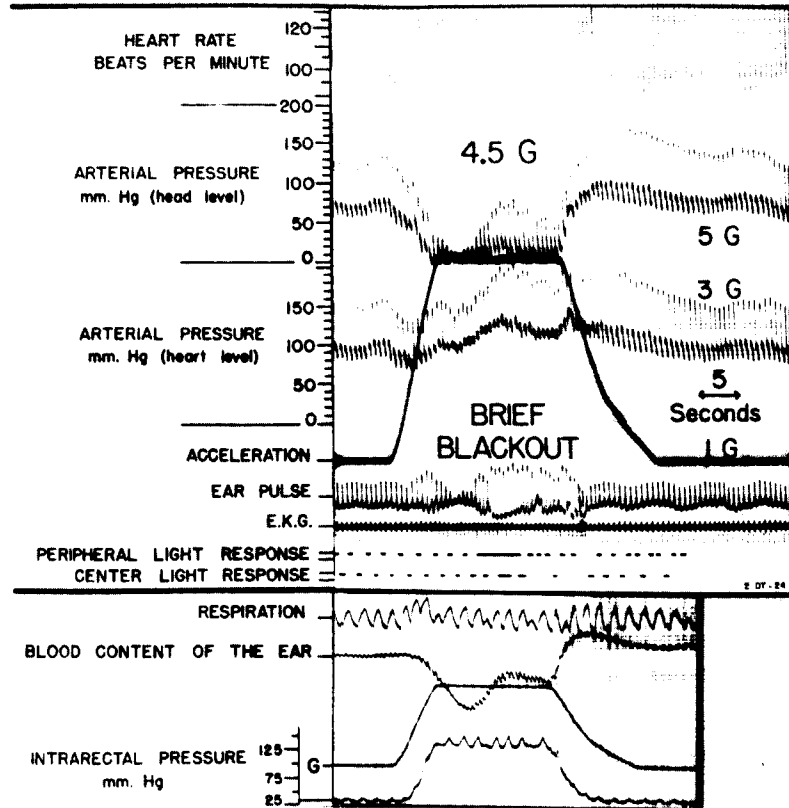


Figure 4.— The recordings were made by two photokymographic cameras operating simultaneously, one mounted in centrifuge cockpit (lower panel) and one in recording room adjacent to centrifuge (upper panel). Vertical white lines on upper panel delineate 5-sec intervals and were 15 mm apart before photographic reduction. Black acceleration line indicates the magnitude of headward acceleration in g units. Simultaneous recording of acceleration (indicated as g in lower panel) serves to synchronize the two recordings. Length of black lines designated as peripheral and center light response indicates subject's reaction time to light signals in peripheral and central fields of vision, respectively.



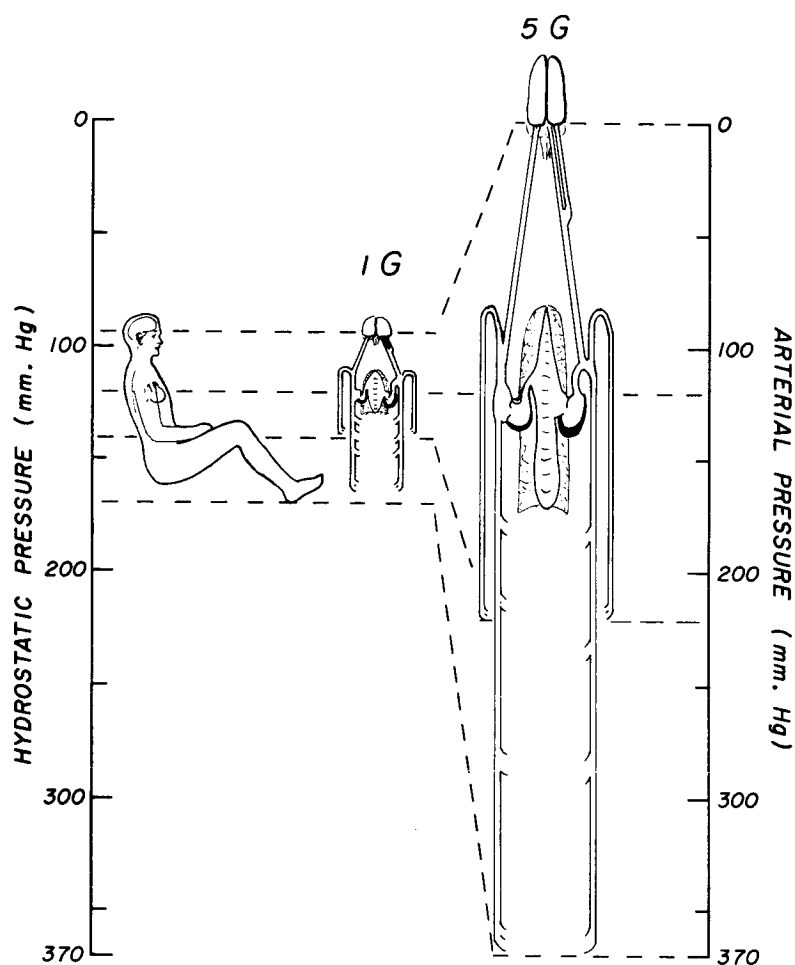


Figure 5.— Diagrammatic representation of hydrostatic pressures in vascular system of a man in upright sitting position at 1 g and during headward acceleration at 5 g. First figure (left) shows average position of pilot in presentday aircraft. Second figure (center) is a diagrammatic representation of vascular system of this pilot at 1 g, indicating that, with an arterial pressure of 120 mm Hg at heart level, arterial pressures at head and foot levels are calculated to be 96 and 170 mm Hg, respectively. Third figure (right) demonstrates the fivefold increase in differences in hydrostatic pressure imposed by 5 g of headward acceleration. Assuming that arterial pressure at heart level was maintained at 120 mm Hg, arterial pressure at base of the brain would be zero, while at the heels it would be 370 mm Hg. Under this circumstance and in the absence of muscular activity, a venous pressure of 250 mm Hg would be required to return blood from the heels to the level of the heart. See figure 4 for verification of these differences in arterial pressure at heart and head levels with subject in upright seated position at 1 g and during exposures to headward acceleration.

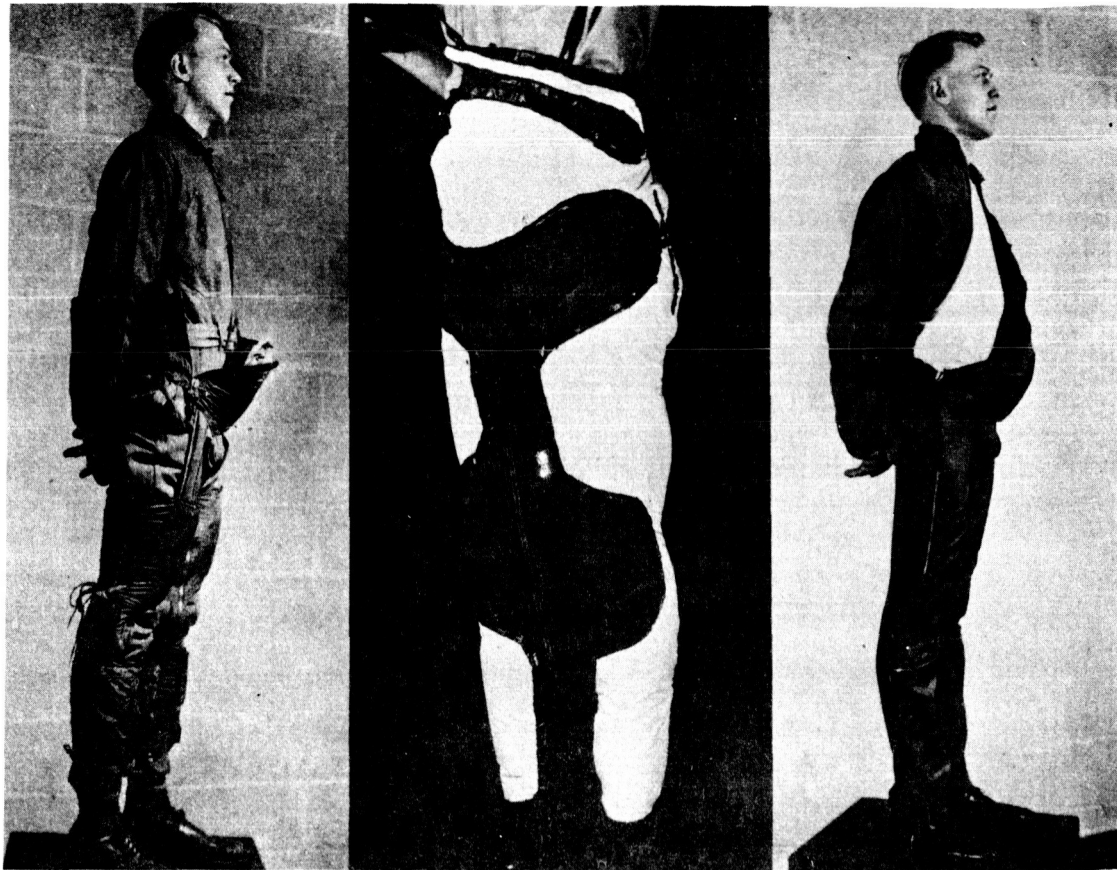


Figure 6.— Bladder system for simultaneous application of pressure to the calves, thighs, and abdomen. This relatively simple system is designed to be inflated to a single pressure and can be incorporated into any type of garment that will ensure relatively efficient transmission of the bladder pressure to the desired surfaces of the body. The bladder systems of all currently used antiblackout suits, of which this is the precursor, are closely similar to the system illustrated. This is illustrated by the "skeleton" suit shown in the left panel of this figure and by the full coverall suit on the right, which was used during World War II by U.S. Navy pilots. This system was devised by Mr. David M. Clark, formerly of Worcester, Massachusetts. A historical review of the development of antiblackout suits prior to and during World War II has been prepared by Thomas W. Walker in "Blackout! The Development of the Anti 'G' Suit. 'G' Suit Pioneers in the U.S., Germany, Australia (1939-42)." Aerotec Industries Review. Autumn, 1959, pp 4-6.

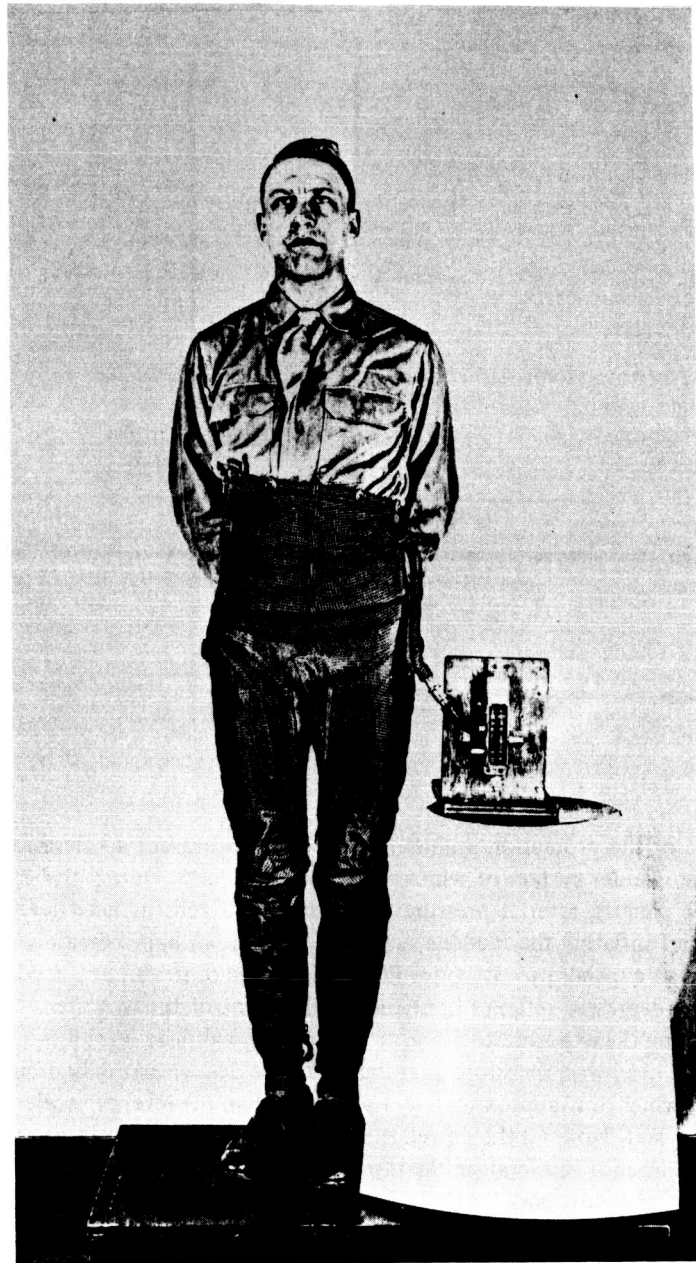


Figure 7.— The M-21 antiblackout suit and its associated pressure control valve. This was one of the first suits incorporating the single pressure bladder system shown in figure 6 whose effectiveness as an antiblackout device was studied extensively on human centrifuges and which was subsequently used by the United States Air Force.

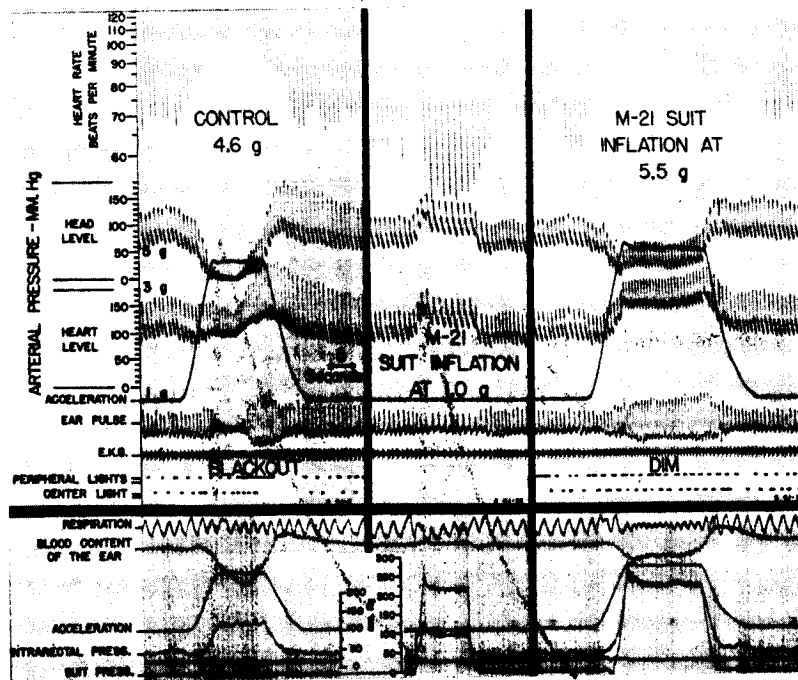
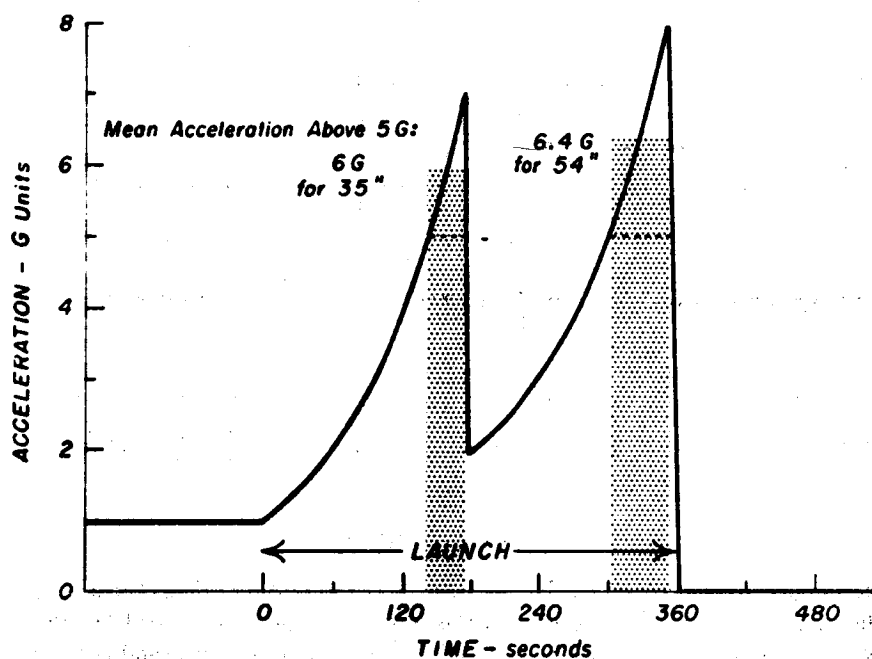


Figure 8.— An example of the protection against the effects of headward acceleration afforded by inflation of an antiblackout suit, the bladder system of which is shown in figure 6. During the control exposure of this normal subject to 4.6 g (left panels), arterial pressure was reduced to zero at head level, and complete loss of vision resulted. The effects of inflating the bladder system of the suit to approximately 225 mm Hg at 1 g and to the same pressure during an exposure to 5.5 g are illustrated in the center and right panels, respectively. Pronounced bradycardia and other depressor reflexes limit the development of the hypertensive effect produced by inflation of the suit at 1 g. During the exposure to 5.5 g, arterial pressure at head level was increased to 200/140 mm Hg or more; perfusion of the head was, therefore, maintained to the degree that only dimming of vision occurred at this level of acceleration, which was approximately 1 g greater than the level of acceleration producing complete loss of vision without the suit. Note (i) the correlation between the intrarectal (intra-abdominal) and suit pressures (lower panels); at this level of acceleration the intra-abdominal pressure was only slightly less than the pressure in the bladder system of the suit, and (ii) the decrease in amplitude of respiration at 5.5 g caused by the high intra-abdominal pressure that elevates and restricts movements of the diaphragm. (See legend of fig. 4 for detailed explanation of tracings.)



\* Copied from Figure 9-5, Results of the First United States Manned Orbital Space Flight  
February 20, 1962

Figure 9.— Acceleration profile of launch phase of John Glenn's orbital flight. Stippled areas show periods of acceleration greater than 6 g. (Copied from fig. 9-5, of Manned Spacecraft Center, National Aeronautics and Space Administration. Results of the First U.S. Manned Orbital Space Flight, Feb. 20, 1962.)

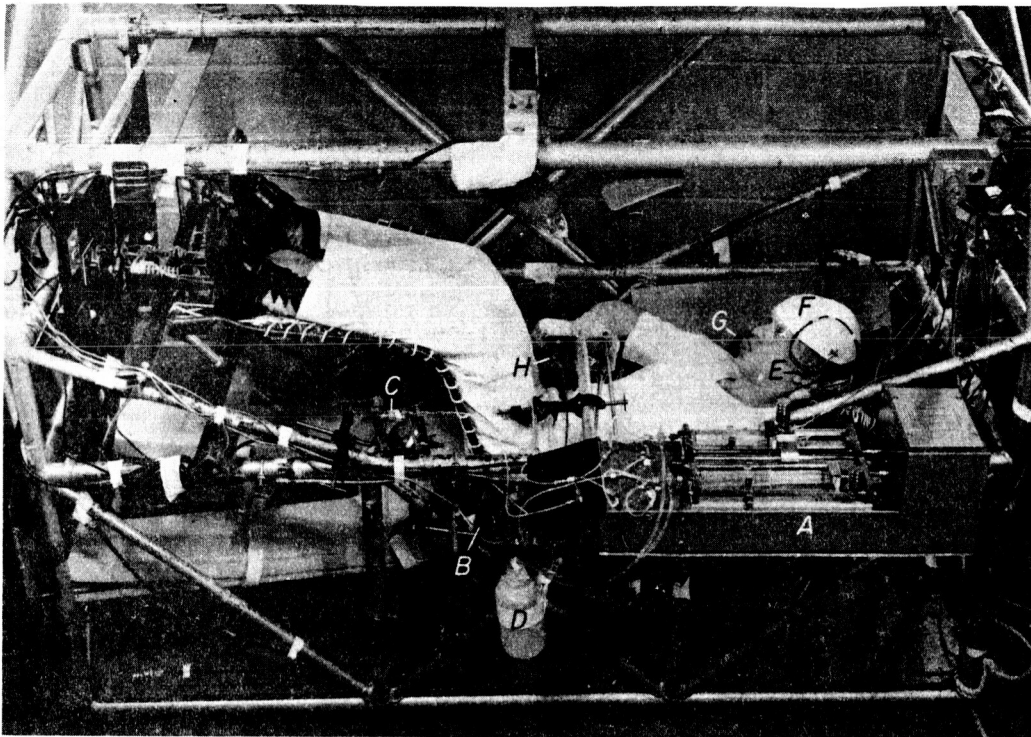


Figure 10.— Subject in place in supine-sitting position used during forward acceleration. The torso is inclined  $12^{\circ}$  forward, the hips flexed  $100^{\circ}$  from the torso and the knees flexed  $100^{\circ}$  from the thighs. Key to labels: A, withdrawal-infusion syringe; B, cuvette oximeter; C, strain gauge and tubing; D, plastic discard bottle, E, ear oximeter fixed firmly to heat-flushed pinna of ear by plaster helmet, F; G, mouthpiece containing thermocouple, H, control panel operated by subject's right hand. The left forearm and hand, containing the radial artery and right atrial catheters, were supported by a special arm board not visible in the picture.



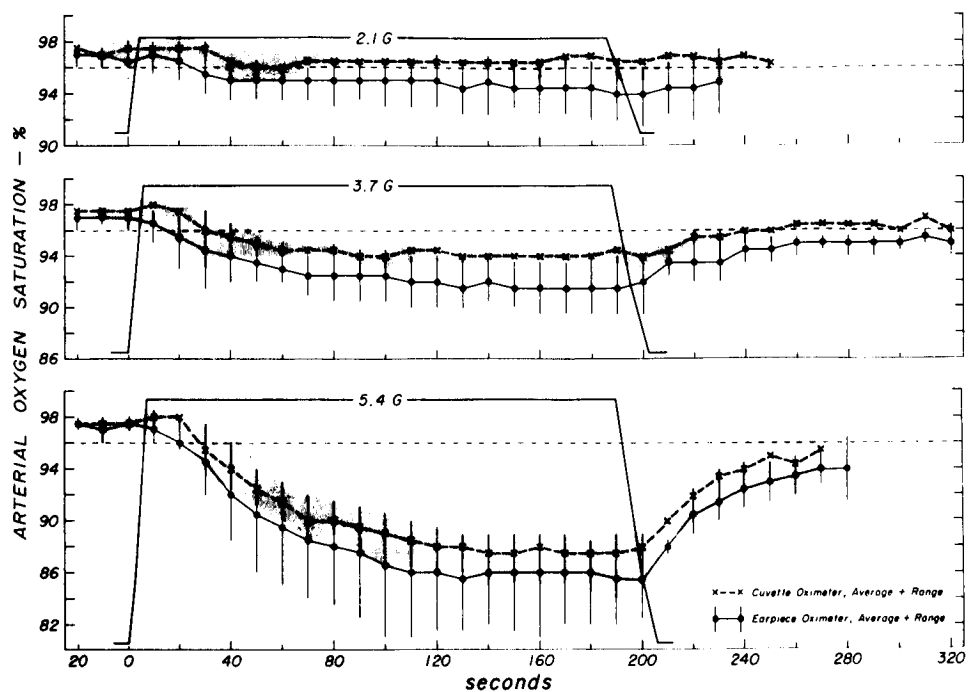


Figure 12.— Average and range of changes in arterial oxygen saturation of four healthy men, recorded by cuvette and ear oximeters during 3 min at 2.1 to 5.4 g, breathing air.



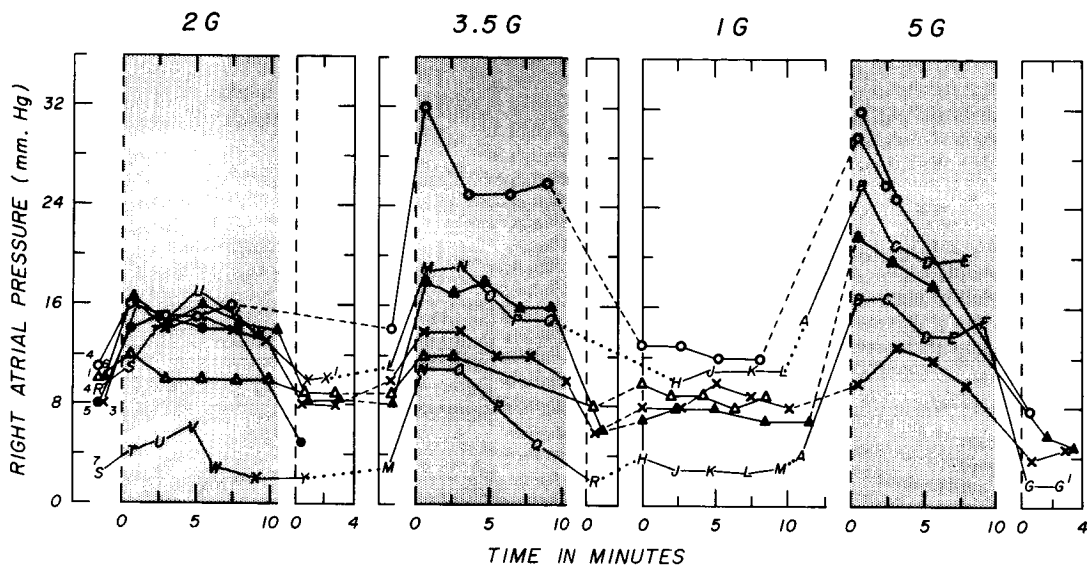


Figure 13.— Effect of forward (transverse) acceleration on right atrial pressure in six healthy subjects in the seated supine position. Note (i) the increasing magnitude of the increment in atrial pressure with increased levels of acceleration; (ii) the progressive decrease in right atrial pressure in the course of the 10-min exposure from the maximal level attained at the onset of acceleration; and (iii) the systematic decrease in right atrial pressure at 1 g immediately after exposure in relation to the value of 1 g before each exposure. This suggests a loss of circulating blood volume during the exposure or an increased capacity of the vascular bed, or both. The values that are plotted as symbols were obtained in temporal sequence as indicated on the abscissa. The two sets of values plotted as letters were obtained in the temporal sequence indicated by their numerical position in the alphabet. In these two subjects the initial series of determinations were made at an acceleration of 5 g rather than of 2 g as in the other four subjects. The zero-pressure reference was at midchest level in the third interspace at the sternum.

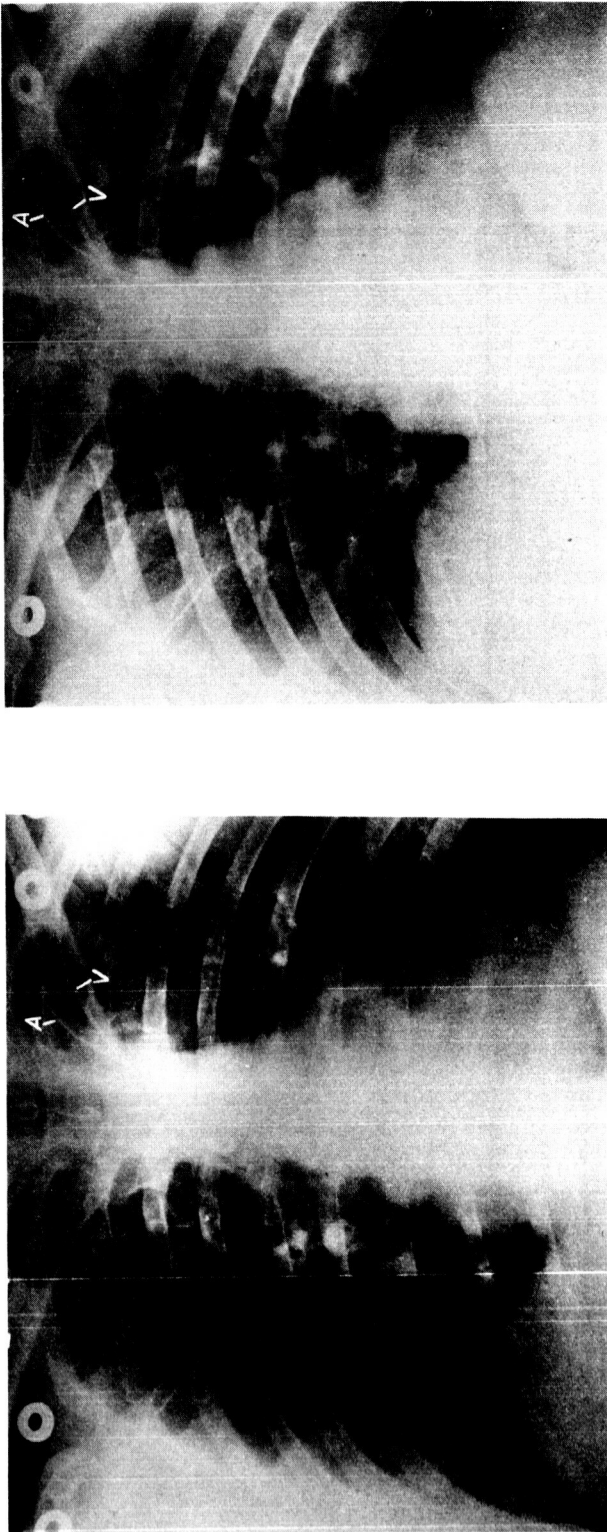


Figure 14.-- Left: A thoracic roentgenogram of normal appearance, obtained just before the subject was accelerated to 5.5 g for 2.33 min while breathing 99.6 percent oxygen. Right: A thoracic roentgenogram of the same subject after termination of the 5.5-g exposure. Note focal areas of increased density, indicative of atelectasis bilaterally, with associated diaphragmatic elevation (A = aortic catheter; V = venous catheter high in the right atrium).

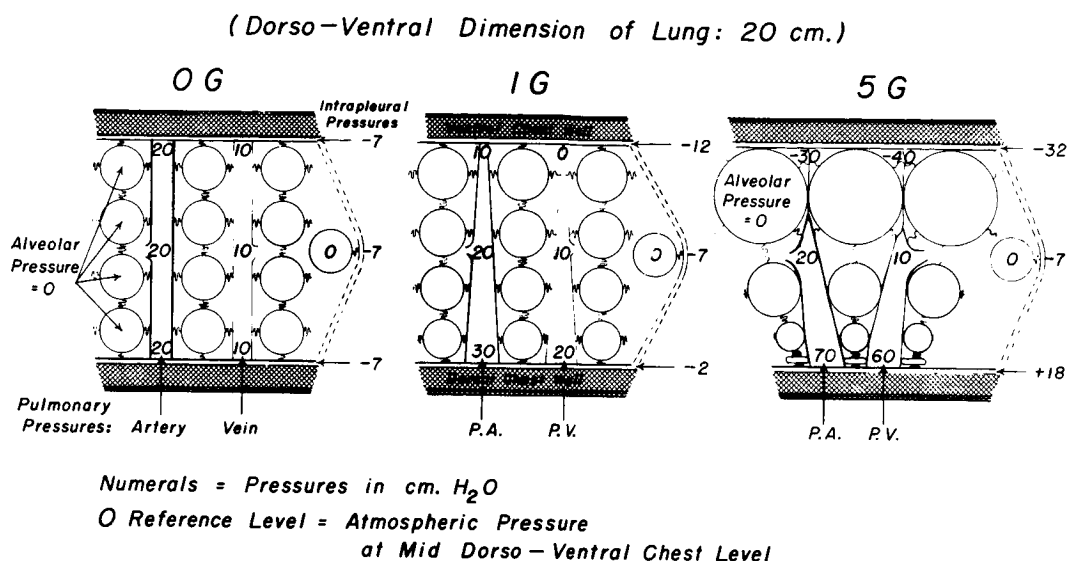


Figure 15.— Diagram of effects of forward (+G<sub>x</sub>) acceleration on intrathoracic pressures (dorsal-ventral dimension of lung equals 20 cm). Numerals indicate pressures as cm H<sub>2</sub>O and zero reference level equals atmospheric pressure at midlung coronal plane. In the absence of obstruction of the airway, pressure in alveoli (represented as open circles) would be approximately equal to ambient atmospheric pressure and would be the same in all alveoli, independent of level of acceleration or position of alveoli in the thorax. Mean pulmonary arterial, pulmonary venous, and intrapleural pressures at midlung level are assumed to remain constant at 20, 10, and -7 cm H<sub>2</sub>O, respectively, during exposure to 0, 1, and 5 g. Intrapleural pressures shown at ventral (superior) and dorsal (dependent) surfaces of the lungs at 1 and 5 g were calculated by assuming that the thoracic contents react to the change in weight caused by acceleration in a manner similar to that of a fluid with a specific gravity of 0.5. These estimated pressure values are similar to end-expiratory pressures actually recorded at these sites in dogs exposed to 1 and 5 g in the supine horizontal position.

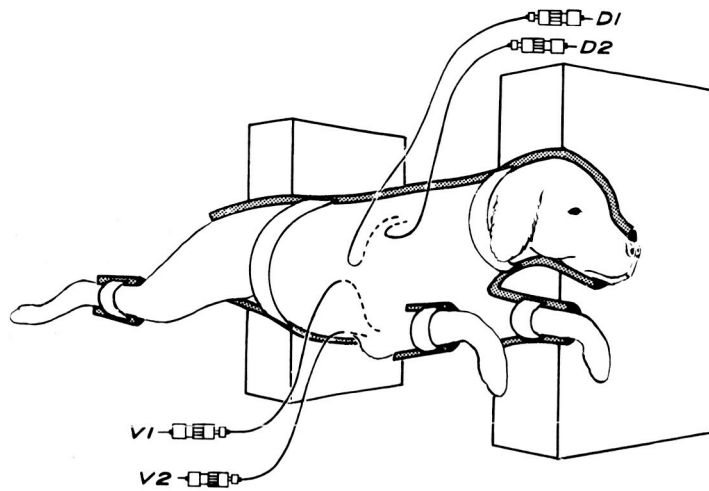


Figure 16.— Assembly for studying intrapleural pressures at different sites in thorax of dog in different body positions. Note dorsal (D) and ventral (V) placement of catheters.

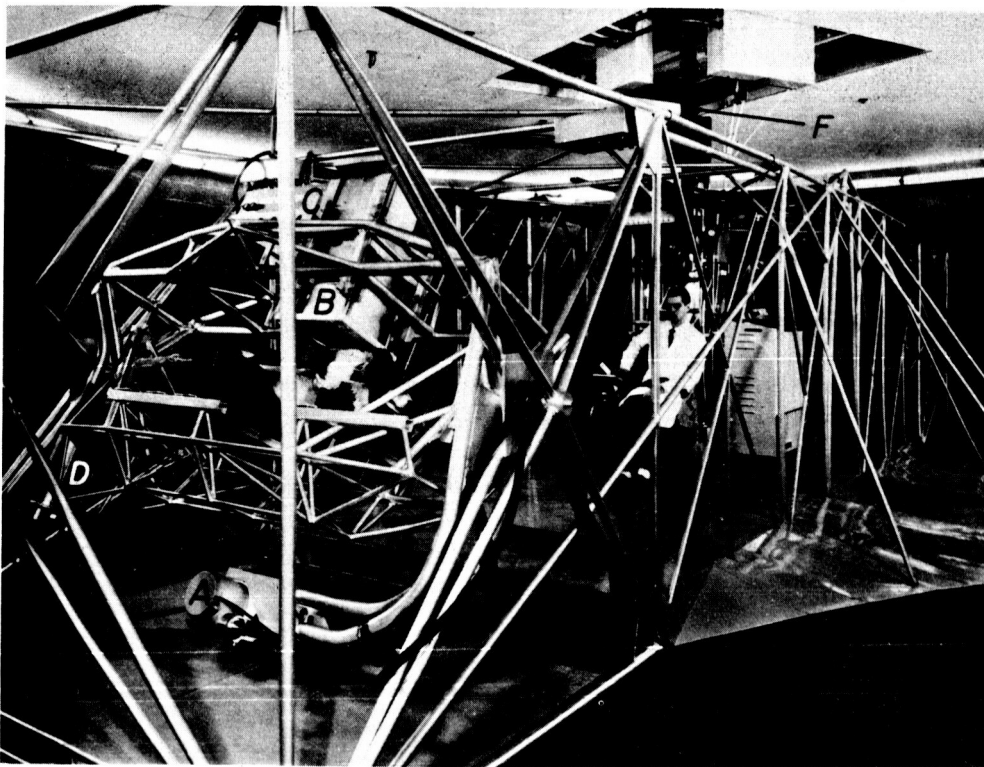


Figure 17.— Special cockpit assembly for measurement of intrapleural pressures in dogs at different positions while exposed to different g levels, showing equipment for biplane roentgenography. A = X-ray tube; B = image intensifier; C = image-orthicon camera; D = counterweight; F = commutator through which signals from equipment in cockpit are transmitted to recording equipment in another room.

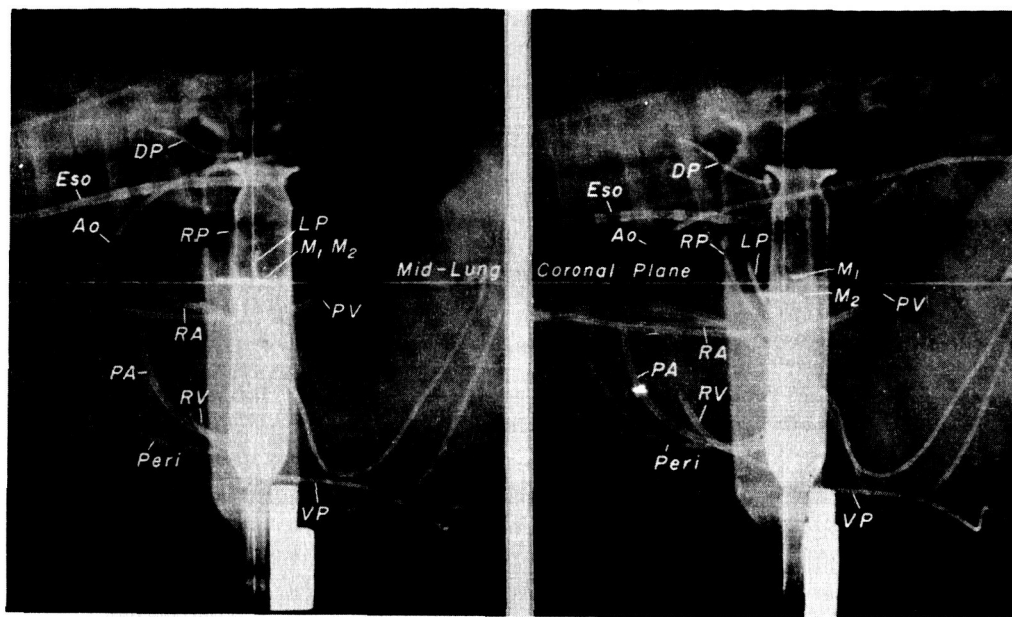


Figure 18.— Lateral roentgenograms of thorax of a dog showing catheter positions for study of intrathoracic pressures during backward ( $-G_x$ ) acceleration. Left Panel,  $-1 G_x$  (prone body position). Right Panel,  $-6.4 G_x$ . The dog is supported by a molded half-body cast, whose thoracic part is made of clear plastic (Lucite) for inspection and better X-ray penetration. Intravascular catheters: RA, right atrium; RV, right ventricle; PA, main pulmonary artery; Ao, aortic arch; PV, left atrial (transeptal) in a pulmonary vein. Extravascular catheters: DP, dorsal pleura; VP, ventral pleural; RP, right pleural; LP, left pleural; Eso, esophageal; Peri, pericardial. Thistle tubes (two vertical glass cylinders, containing Ringer's solution, on either side of the dog's chest) are visible. Their menisci  $M_1$  and  $M_2$  visualized by floats containing lead, are adjusted at 1 g to midlung coronal plane, which is marked on the cassette by a horizontal steel wire. During  $-6.4 G_x$  acceleration, the position of the menisci indicates that the cockpit floor was not quite perpendicular to the resultant acceleration (overtilt  $< 1^\circ$ ).

(Dog-20 kg., Supine Horizontal Position, Morphine-Pentobarbital Anesthesia)

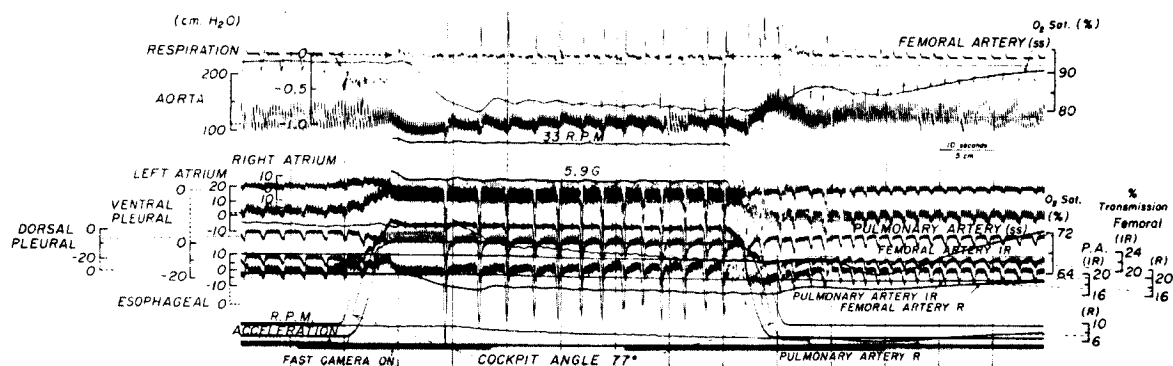


Figure 19.— Simultaneous recording of oxygen saturation and opacity at 800 nm (hemoglobin concentration) of mixed venous and systemic arterial blood and of circulatory, intrapleural, and related intrathoracic pressures in an anesthetized (morphine-pentobarbital) 20-kg dog during a 1-min exposure to a forward (+G<sub>x</sub>) acceleration of 5.9 g. Dashed pressure calibrations show zero reference line for the pressure transducer systems when exposed to acceleration. Zero reference level for vascular pressure is midthoracic coronal plane. Pleural and esophageal pressures are referred to ambient pressure at the level of the respective catheter tips, as determined by lateral and anteroposterior thoracic roentgenograms. Correct zero reference levels for the manometer systems are not given for periods of tangential acceleration associated with starting and stopping the centrifuge, indicated by double-ended dashed arrows. Note: (i) decrease in arterial oxygen saturation during first 20 sec of the exposure, indicative of the presence of a large pulmonary arteriovenous shunt; (ii) progressive decrease, during the exposure, of transmission of infrared light (800 nm) by systemic and pulmonary artery blood, suggesting the occurrence of hemoconcentration probably due to edema formation in dependent regions of vascular system.

(MEAN VALUES OF 7 DOGS - Level of Sixth Vertebra)

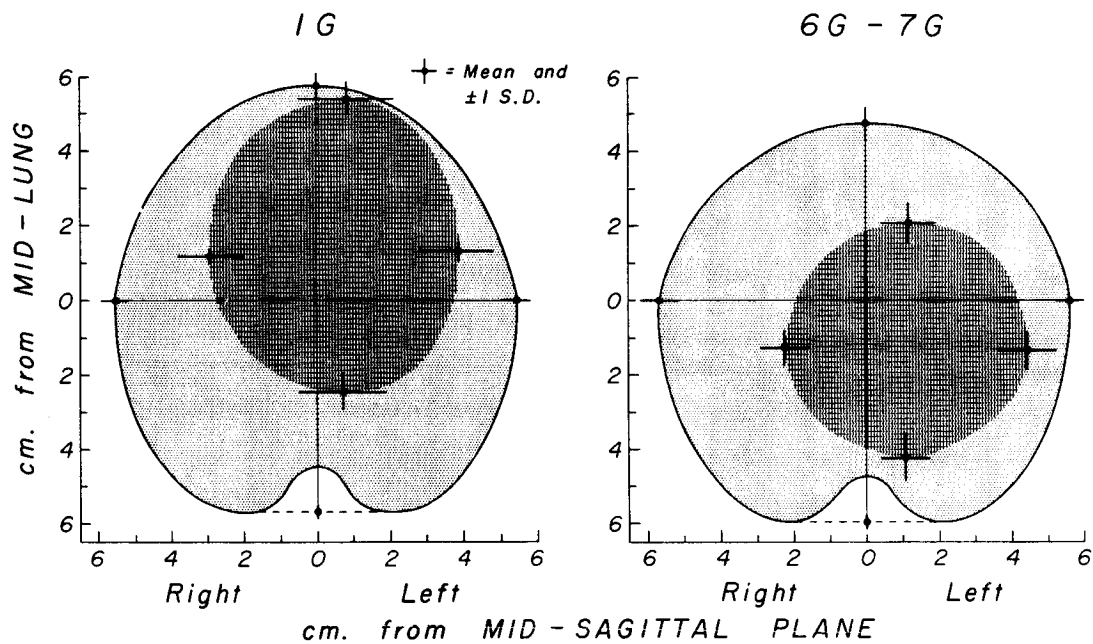


Figure 20.— Mean and standard deviation of distortion and displacement of heart and lungs in seven dogs by exposure to an acceleration of 6 to 7  $+G_x$ . Note that the normally thin region of lung parenchyma between the ventral border of the heart and the chest wall at 1 g (left panel) is apparently distended during exposure to 6 to 7 g (right panel) to occupy a large portion of the cross-sectional area of the chest. This is caused by the centrifugation of the higher specific gravity heart and blood towards the dependent portions of the thoracic cavity, which results in highly negative retrosternal intrapleural pressures which develop during acceleration. Since the level of atmospheric pressure distending the alveoli is undiminished during acceleration, a large increase in transmural alveolar pressure occurs and is responsible for the disruption of pulmonary parenchyma which has been observed under these conditions.

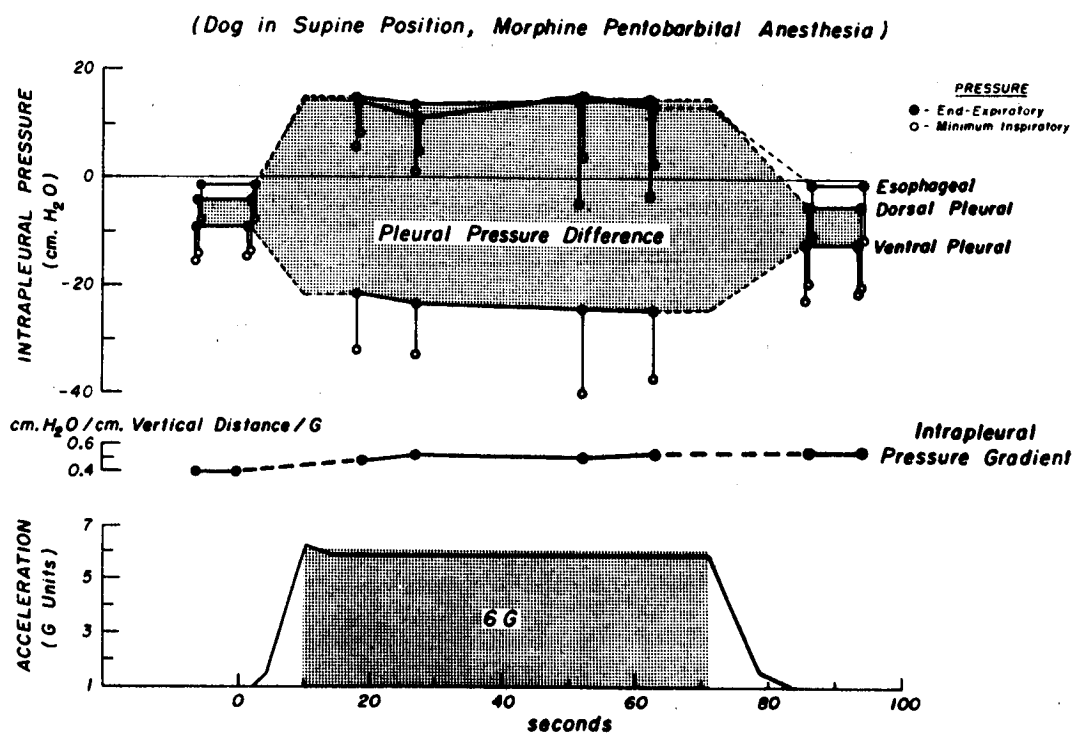


Figure 21.— Variations in intrapleural pressures with changes in weight produced by forward ( $G_x$ ) acceleration.



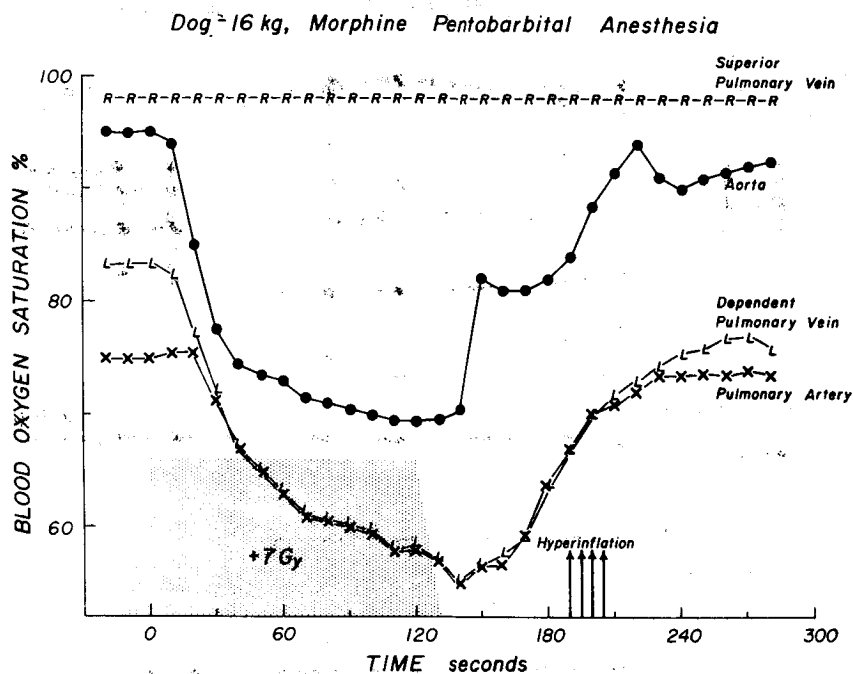


Figure 22.— Differential effects of acceleration in left decubitus position ( $-G_y$ ) for 120 sec on oxygen saturation of systemic arterial blood and pulmonary venous blood draining superior (right) and dependent (left) lung in 16-kg dog (morphine-pentobarbital anesthesia) breathing air. Values for saturation of blood from superiorly positioned right lower lobe (shown by R) remained normal throughout the exposure, while those of blood from left lower lobe (L) decreased to level of pulmonary arterial (mixed venous) blood (X), indicating a 100 percent arterial-venous shunt in dependent regions of lung. Saturation of left pulmonary venous blood was abnormally low before exposure to acceleration and remained low after exposure, in spite of repetitive hyperinflation of lung to an airway pressure of 30 cm H<sub>2</sub>O. Subsequently, left pulmonary venous saturation returned to normal when dog was rotated to right decubitus (left lung superior in chest) and persistent partial desaturation of pulmonary venous blood from right (dependent) lung developed.

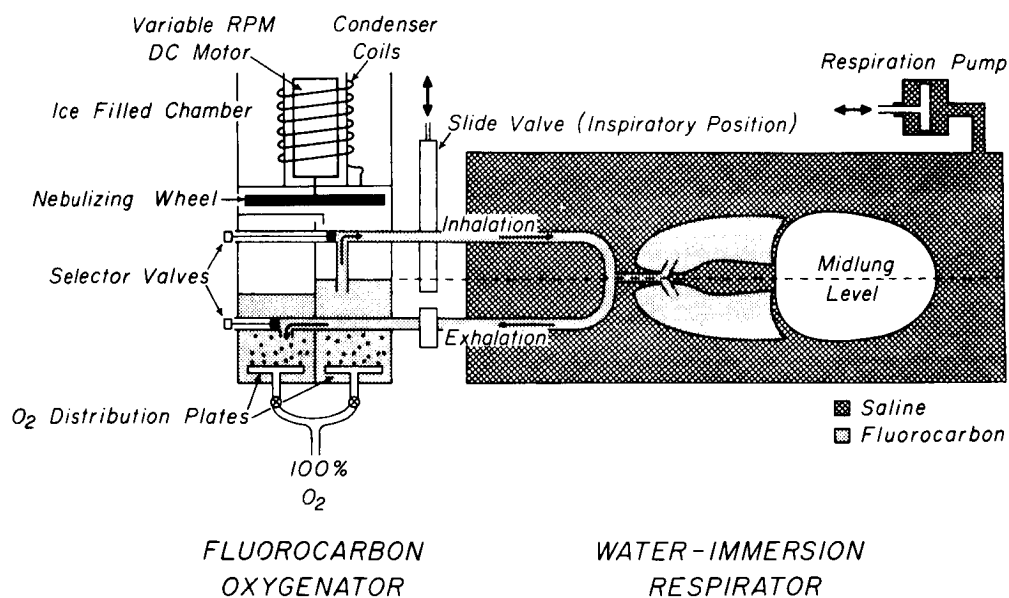


Figure 23.— Representative drawing of the water-immersion respirator and fluorocarbon-oxygenator assembly for liquid-breathing studies in dogs. Pneumatically actuated slide valve, electrically synchronized to respiration pump, directs flow of room air or fluorocarbon, determined by selector valves, through 1 inch Lucite inhalation and exhalation lines. Dead space is minimized by connecting Lucite Y directly to endotracheal tube. Three sintered stainless-steel plates distribute oxygen flow over a large area near the bottom of the inhalation and exhalation chambers to partially oxygenate the fluorocarbon. Complete oxygenation and carbon dioxide removal is accomplished by continuously circulating preoxygenated fluorocarbon from the exhalation chamber over the nebulizing wheel to the inhalation chamber. Fluorocarbon is circulated by a centrifugal pump (not shown) in the bottom center of the oxygenator driven by a shaft extension from the nebulizing wheel.

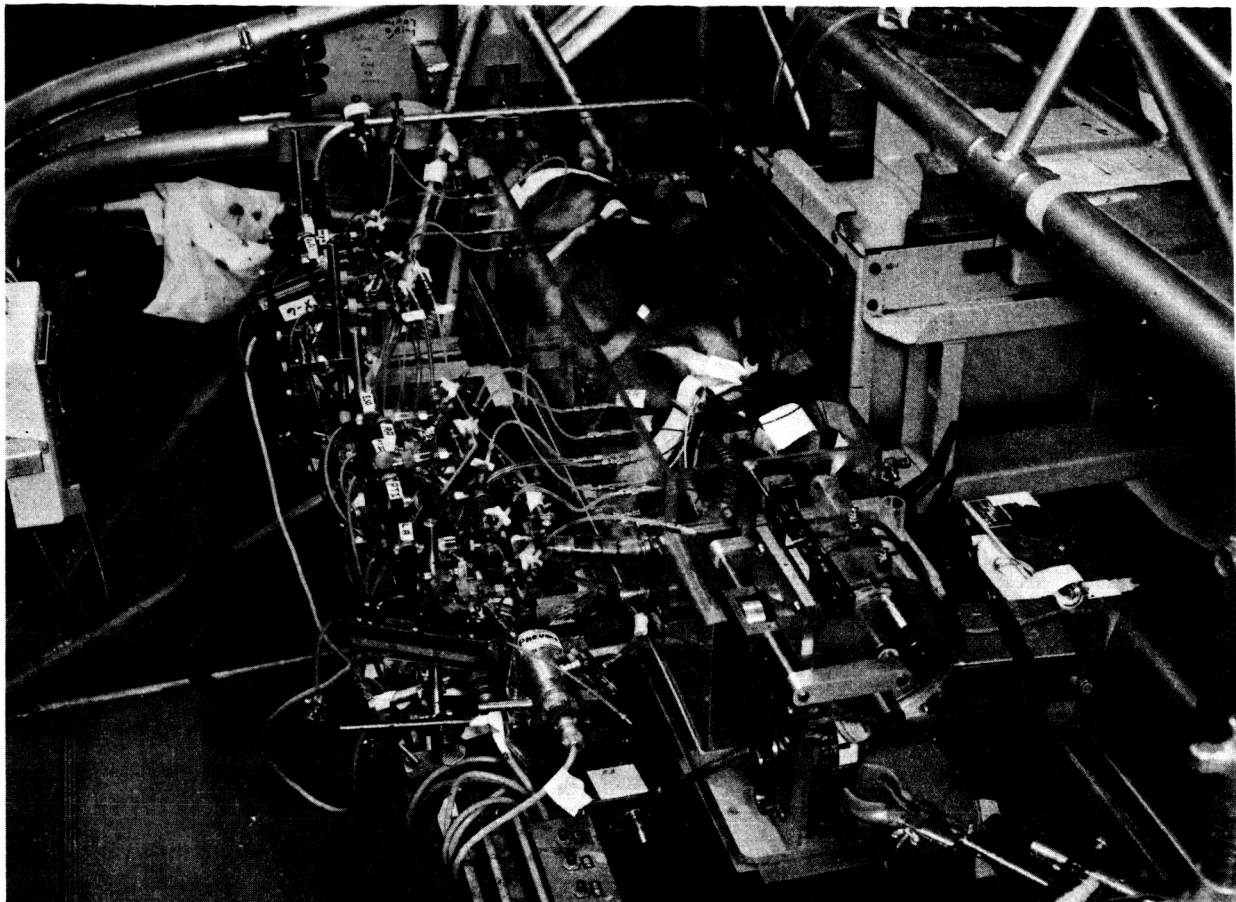


Figure 24.— Water-immersion liquid-breathing apparatus mounted in the centrifuge cockpit. Dog positioned left side down in the immersion tank, with head nearest the camera. At this time, the dog was restrained only by pelvic and shoulder straps and breathed room air spontaneously. Later, the dog was immersed in saline. The respiration pump in the foreground withdraws a tidal volume of saline from the immersion tank on inspiration and returns the saline to the tank on expiration. The small Lucite tank beneath the respirator pump contained fluorocarbon during the liquid-breathing part of the experiment which followed. The row of catheters from ports along the side of the immersion tank are connected to individual strain gauges through hydraulically actuated valves. The valves permit flushing the catheters and inserting calibration pressures in the strain-gauge lines from a remote station during rotation of the centrifuge. X-ray source and image intensifier used to obtain biplane films and video images are shown in the left- and right-hand margins, respectively.

(DOG 10.3 kg, MORPHINE - PENTOBARBITAL ANESTHESIA)

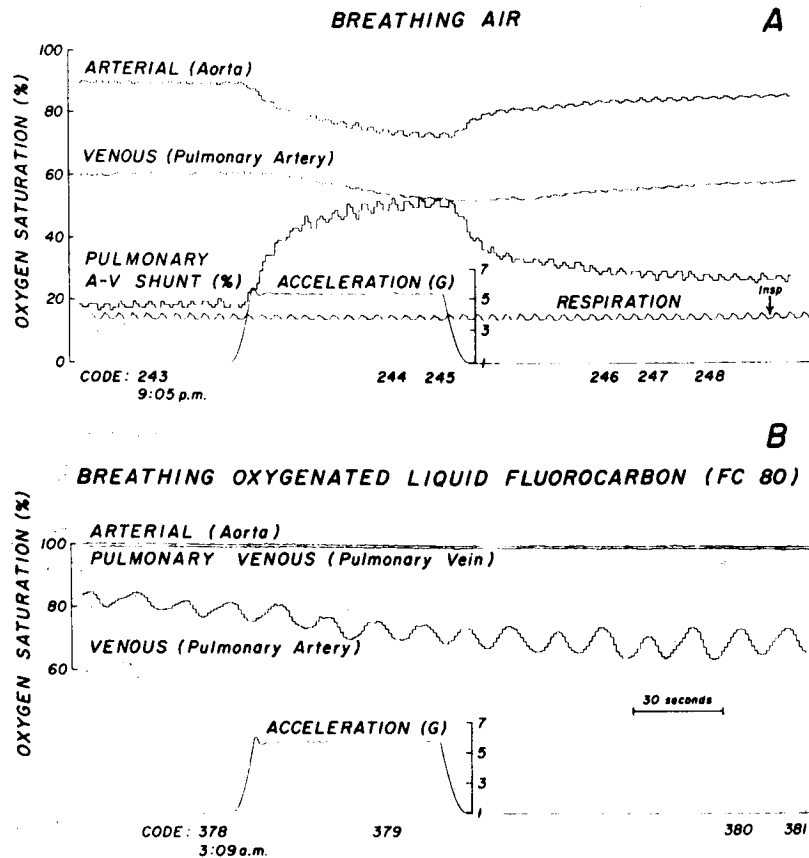
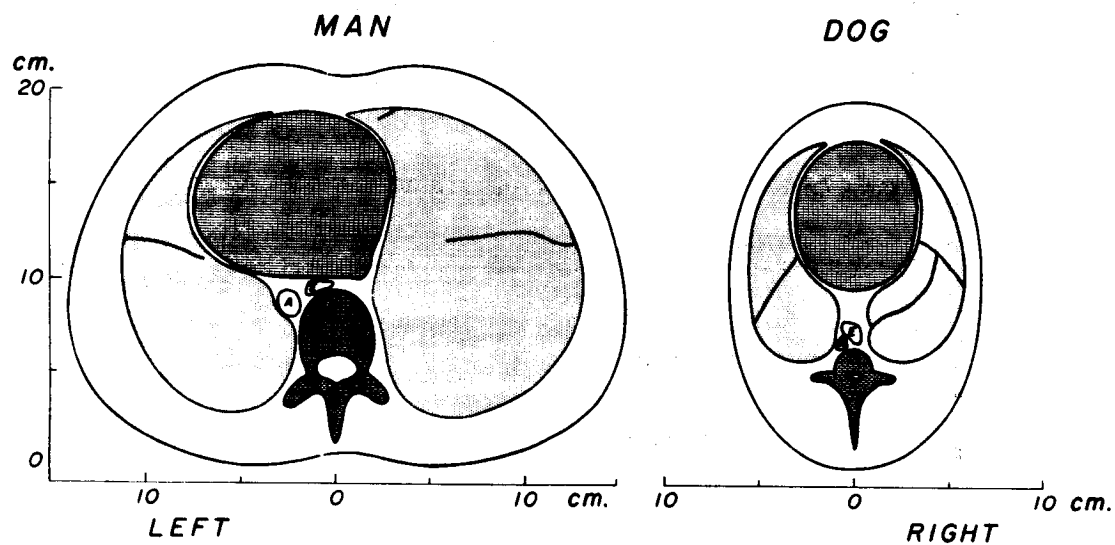
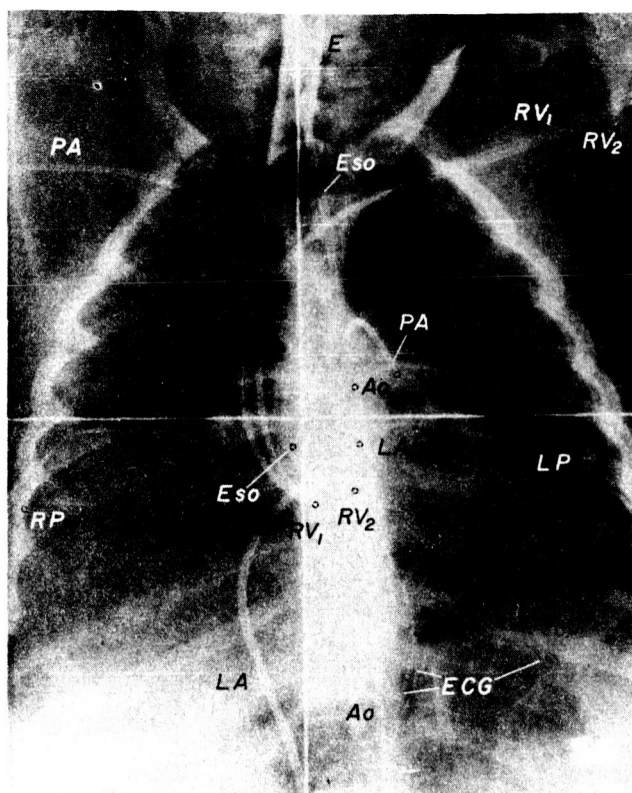


Figure 25.-- Computer (Calcomp) plot of oxygen saturation during 1-min exposures to  $+G_y$  acceleration when (A) breathing air, immersed in water, and (B) breathing oxygenated liquid fluorocarbon, immersed in water. The decrease in the pulmonary artery blood oxygen saturation during the acceleration plateau in (B) was probably due to the steady decrease in oxygen content of fluorocarbon contained in the 4-liter rebreathing compartment. The oxygenator was promptly reconnected to the breathing compartment after the centrifuge stopped rotating, and the pulmonary artery saturation gradually returned to the preacceleration value. The sinusoidal variations in the oxygen saturation of the mixed venous (pulmonary artery) blood are at respiratory frequency and result from the changes in cardiac output associated with the sinusoidal variations in pressure applied to the dogs total surface area by the respiration pump.



**Figure 26.— Comparison of dimensions and topographic relationships in thorax of humans and dogs (cross section at level of sixth vertebra).**

( ♀ Chimpanzee 39 kg, Sernylan-Pentobarbital Anesthesia )



**Figure 27.**— Anterior-posterior (A-P) roentgenogram of the thorax of female chimpanzee F, showing location of catheters for recording pleural and intrathoracic circulatory pressures during exposures to  $G_y$  acceleration on a centrifuge. Definition of symbols follows:  $RV_1$  and  $RV_2$  — cardiac catheters with tips positioned in the right ventricular outflow tract and used for injections of indocyanine green dye and isotope-tagged microspheres for determination of the cardiac output and distribution of pulmonary blood flow, respectively; PA — cardiac catheter with tip positioned in pulmonary artery for pressure recordings; Eso — esophageal catheter; RP and LP — pleural catheters with tips positioned at the right and left lateral margins of the lungs, respectively, for pressure recordings; LA — catheter introduced transeptally into left atrium from right femoral vein; Ao — aortic catheter. Wires at bottom margin of thorax are external electrocardiographic leads. This roentgenogram was taken between the series of exposures to  $+G_y$  acceleration during the process of changing the animal from left lateral to the right lateral half-body casts used to support and maintain the body position of the chimpanzee constant in the centrifuge cockpit. The animal had been anesthetized for 11 hr at the time of the roentgenogram.

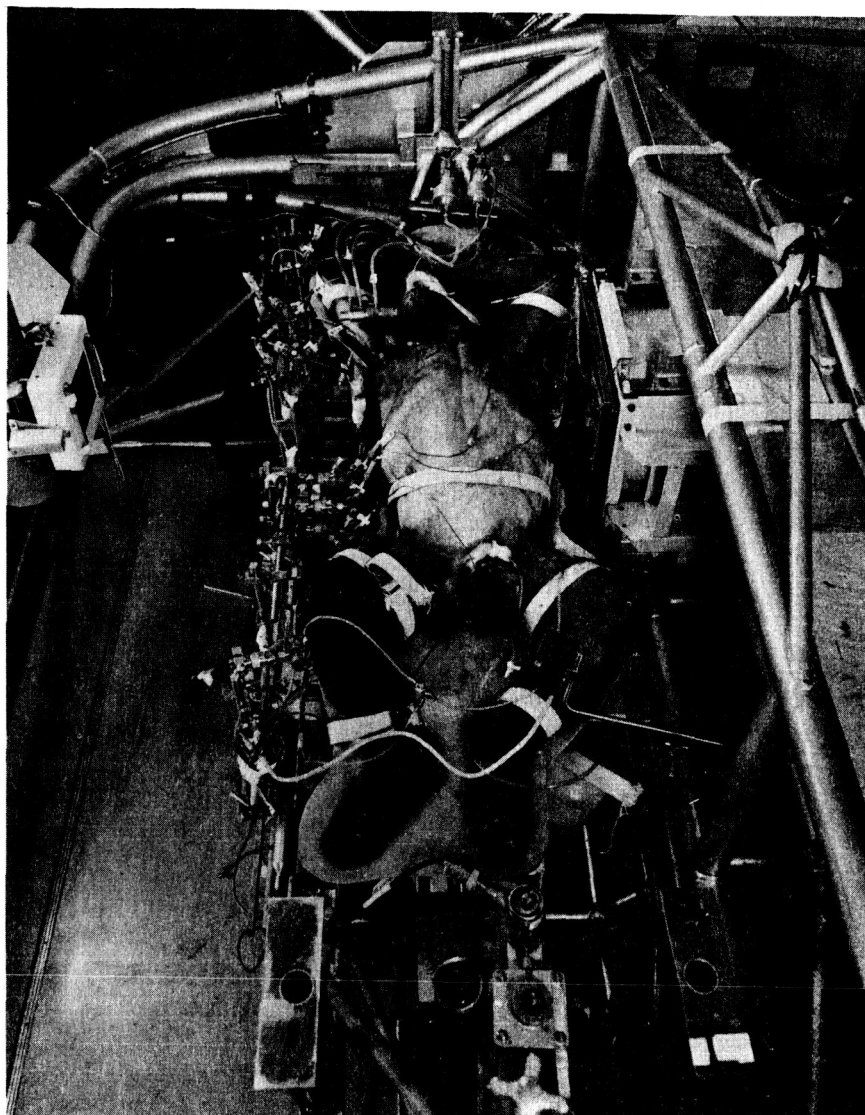


Figure 28.— Photograph of anesthetized chimpanzee lying in a custom-molded fiberglass cast for  $+G_x$  exposure. The cast is attached to a support structure which rotates freely about a horizontal axis. The screw adjustment at the top and very bottom of the photograph is adjusted to align the longitudinal and chest axis of the chimpanzee with the axis of rotation of the support structure. A "U" arm structure supports an X-ray screen (left) and an image intensifier/video camera imaging chain in the other side of the chimpanzee (right). This yoke rotates about the same horizontal axis as the subject support structure and may be positioned to provide lateral or anteroposterior exposures of the thoracic contents. The support structure and X-ray yoke rotate clockwise with increasing speed of rotation of the centrifuge so that the subject always remains exposed to the increasing centripetal force in the same direction independent of the magnitude of the acceleration, that is, speed of rotation of the centrifuge. Along the right side of the chimpanzee are a number of strain-gauges used for measuring intravascular and intrapleural pressures via saline-filled catheters. The strain-gauges are attached by remotely controlled hydraulic valves for interchangeable connection to known pressure sources for calibration of the strain-gauges during the operation of the centrifuge. The pressure signals, electrocardiogram, and roentgen videographic signals are transmitted to the data recording instruments via a mercury trough and metallic slip-ring commutator assembly located on the central axis of the centrifuge.

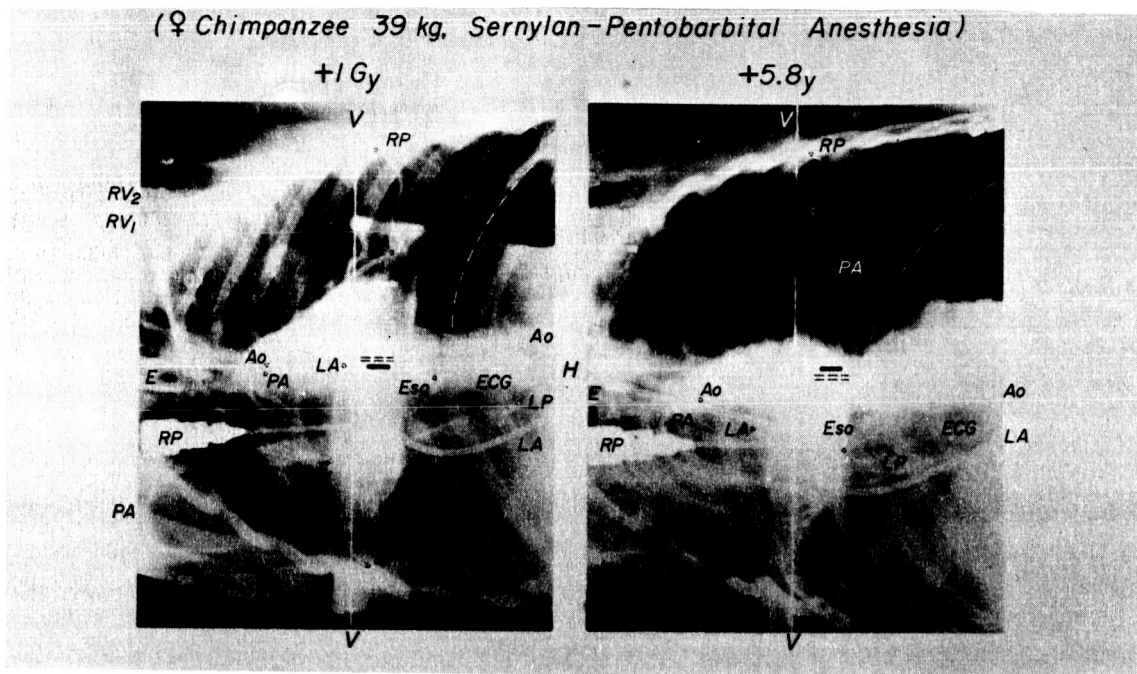


Figure 29.— Effect of lateral acceleration (right side down) on the position of the thoracic contents and tips of the recording catheters in a female chimpanzee. The domes of the diaphragm have been indicated by dashed lines to facilitate visualization of the change in their position produced by exposure to +5.8 G<sub>y</sub>.



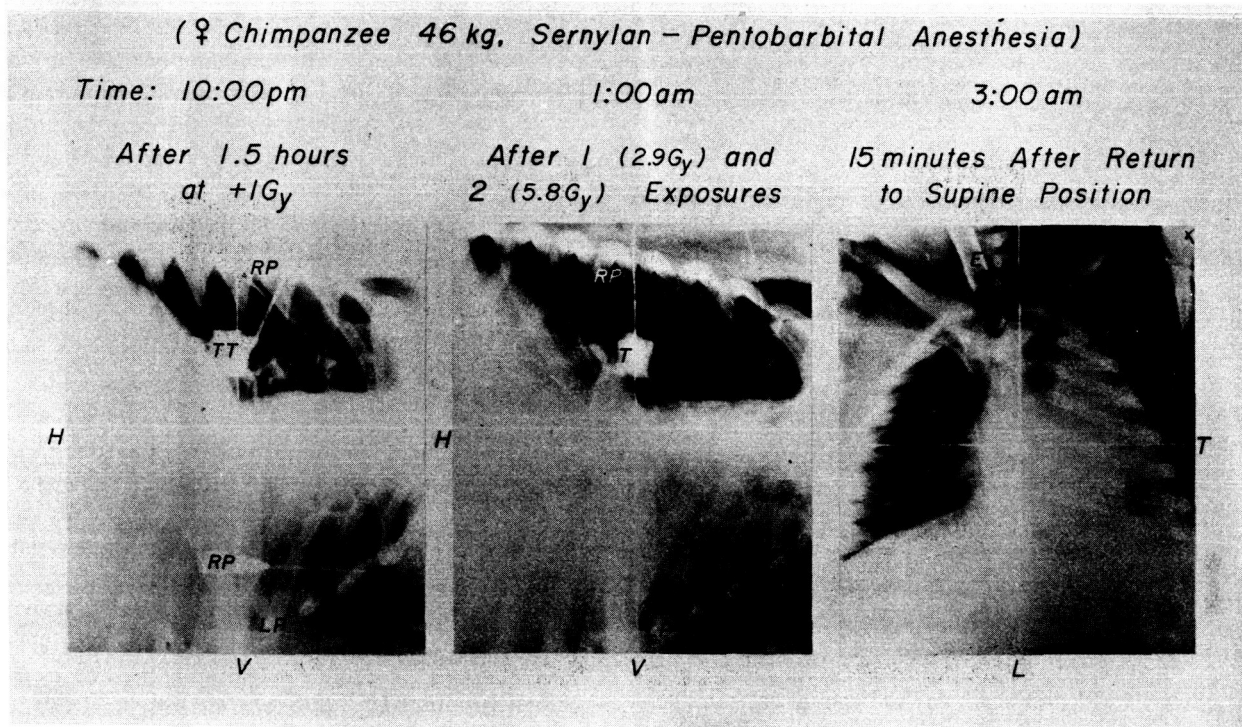


Figure 30.— Posterior-anterior roentgenograms of a female chimpanzee at 1 g before and after 60-sec exposures to 2.9 and 5.8 g in the left lateral (+G<sub>y</sub>) position. T and L mark the silhouettes of steel wires whose intersection falls on the central axis of the roentgen beam. Note: (i) the increase in radiopacity of the dependent left lung after 3 hr at +1 G<sub>y</sub> and three 60-sec exposures to +G<sub>y</sub> acceleration in this body position; (ii) in this animal, unlike most others, roentgen evidence of atelectasis of the left lung persisted after return to the supine position.

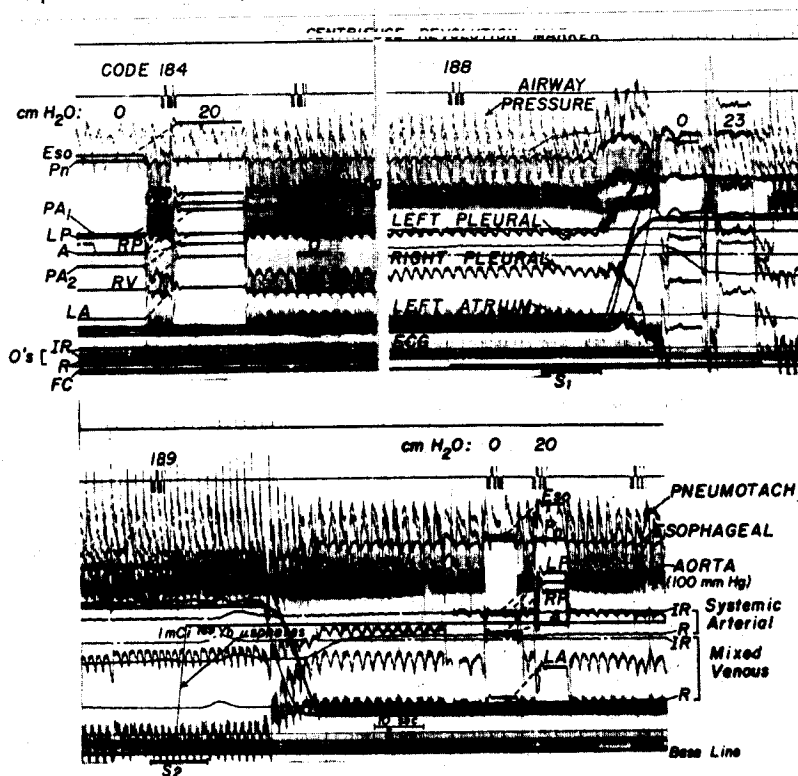


Figure 31.— Original photokymographic recording of multiple physiologic variables before and during an exposure of a chimpanzee to acceleration of  $-5.8 G_y$  for 69 sec.

The recording of the binary decimal codes 184 and 185 during the calibration of the manometer systems at 0 and 20 cm H<sub>2</sub>O and the aortic system (A) at 100 mm Hg (left upper panel), and codes 188 through 192 during the continuous recording encompassing the exposure shown in the right upper panel and continued on the lower panel, identify different events on the recording and are used for synchronizing these events in the parallel recordings on magnetic tape and on the fast camera. The periods when fast camera records (paper speed 25 mm/sec) were obtained are indicated by the black line labeled FC just above the baseline. The abbreviations identifying the various tracings

are as follows: ESO — esophageal pressure; Pn — pneumotachygram; PA<sub>1</sub> — pulmonary artery pressure 1; LP — left pleural pressure; RP — right pleural pressure; A — aortic pressure; PA<sub>2</sub> — pulmonary artery pressure via the second pulmonary artery catheter (this catheter was for sampling of mixed venous blood prior to, during, and after the period of centrifuge rotation); RV — right ventricular pressure (via catheter used for injection of microspheres); LA — left atrial pressure; IR and R in the left upper panel indicate the mechanical zero; that is, zero transmission level of the red and infrared cells of the cuvette oximeters used to continuously record the transmission of red and infrared light of systemic arterial and mixed venous blood from which blood oxygen saturation values were calculated. The numerals 0 and 23 in the right upper panel indicate the periods when the zero-reference levels (thistle-tube zeroes) of the manometers were recorded (and their relative sensitivities to a pressure of 23 cm H<sub>2</sub>O were checked) when the centrifuge was rotating at an average speed of 34 rpm and the centrifuge cockpit was tilted outward to 76° so that the resultant 5.8 g vector of the gravitational-centripetal force was perpendicular to the floor of the cockpit.

The injection of microspheres tagged with 1 mCi of  $^{169}\text{Yb}$ , at S2 in the lower panel, is indicated by the record of the travel of the piston of the remotely activated syringe used to displace the suspended bolus of microspheres into the right ventricle by a trailing high-speed injection of 8 ml of Ringer's solution. Note the increased transmission of red and infrared light recorded in the mixed venous and arterial blood due to the transient dilution caused by this injection. The zero baselines of the manometer systems and their sensitivities were rechecked, as indicated by the numbers approximately 30 sec after the period of centrifuge rotation.

This type of photokymographic recording is useful for monitoring the overall function of the recording systems and associated physiologic events. However, detailed measurements generally cannot be made from this recording because of the slow paper speed coupled with overlap and crossover of the multiple tracings.

SERNYLAN - PENTOTHAL ANESTHESIA  
BREATHING AIR

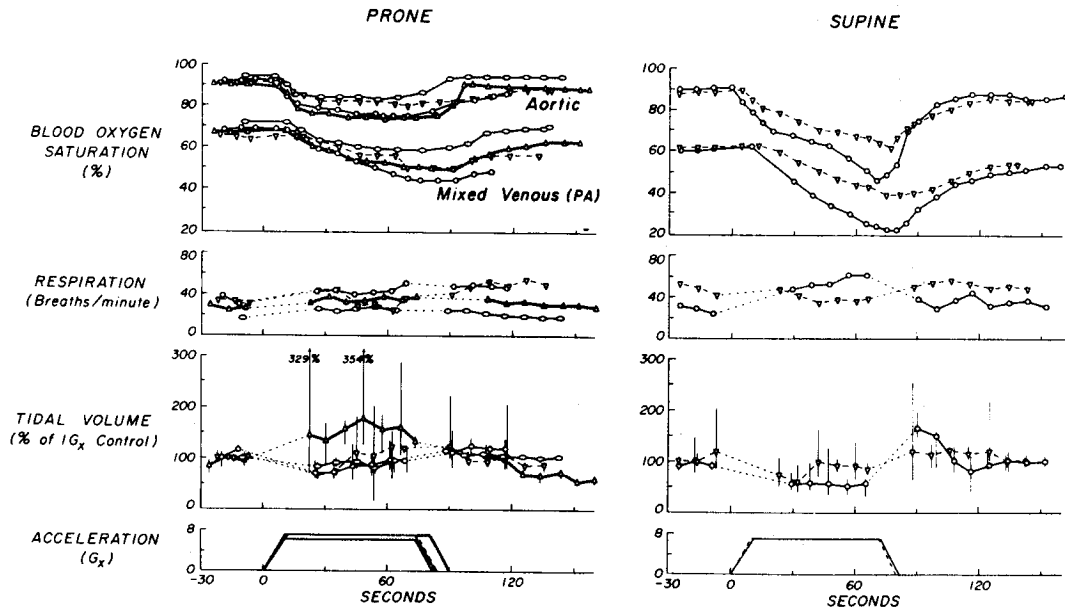


Figure 32.— Changes in oxygen saturation of arterial and mixed venous blood produced by 7.4 G<sub>x</sub> acceleration in anesthetized chimpanzees breathing air. Rapid onset and maintenance of arterial desaturation and delayed and continuing desaturation of mixed venous blood occur during exposure to +G<sub>x</sub> acceleration. Arterial desaturation stabilizes rapidly during acceleration in the prone position, but continues to decrease during exposure to acceleration in the supine position. Respiration rates remained fairly constant throughout exposure to acceleration, but the tidal volume showed decrease in supine position. For further discussion, see text and legend of figure 33.

SERNYLAN - PENTOTHAL ANESTHESIA  
BREATHING 99.6 % OXYGEN

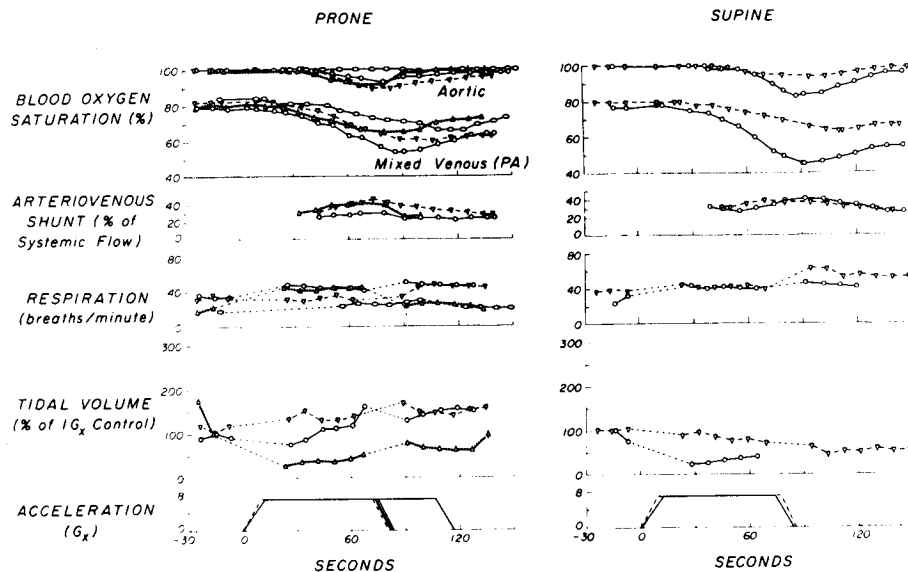


Figure 33.— Changes in oxygen saturation of arterial and mixed venous blood produced by 7.4 G<sub>x</sub> acceleration in anesthetized chimpanzees breathing 99.6 percent oxygen. With onset of acceleration and throughout the maintenance of increased G<sub>x</sub> acceleration as indicated in the lower panels, the blood oxygen saturation decreases continuously until the acceleration is reduced to 1 G<sub>x</sub>. Arterial saturation returns to the normal 100 percent rapidly, whereas the mixed venous oxygen saturation returns to control levels slowly with several minutes delay. The appearance of arterial desaturation and the rapid recovery corresponding to the exposure to increased acceleration is connected with collapse of the dependent alveoli which remain perfused and thereby form a physiological shunt. The magnitude of this shunt expressed as percent of pulmonary blood flow, which is not oxygenated at all, is calculated and shown in the second panels. Respiration rate is increased and tidal volume was variable, increasing or decreasing in different animals in relation to the values prior to acceleration, as shown in the third and fourth panels. The magnitude and duration of desaturation were greater in the supine than in the prone position.

( ♂ Chimpanzee 36 kg, Sernylan-Pentothal Anesthesia )

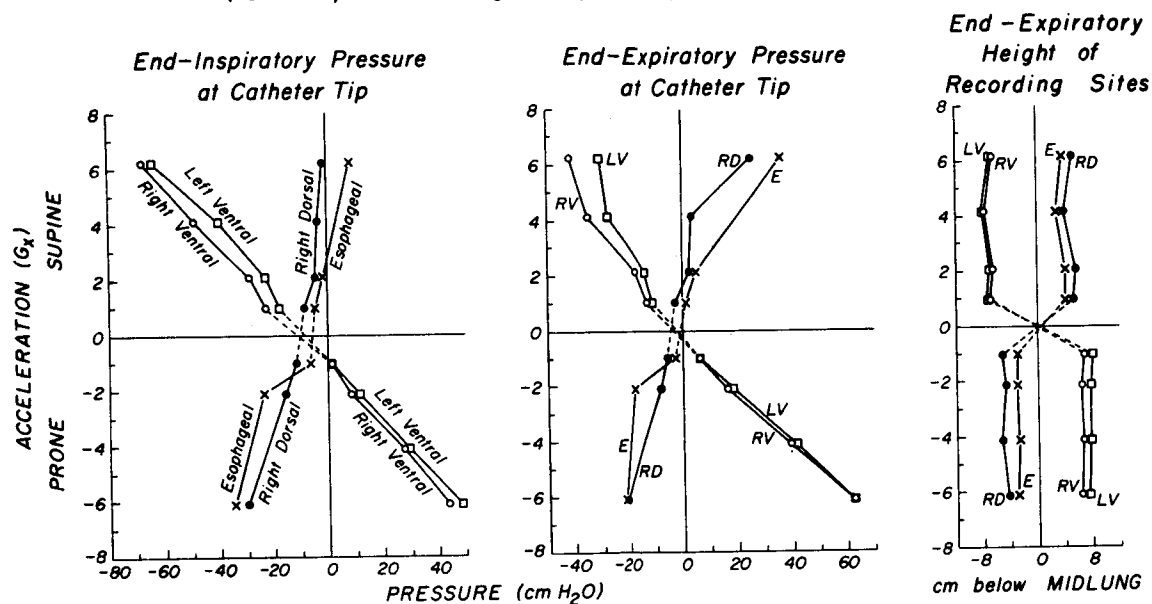


Figure 34.— End-inspiratory and end-expiratory pleural and esophageal pressures during transverse ( $G_x$ ) acceleration of anesthetized chimpanzee.

Intrapleural pressure was always higher in the dependent site relative to the superior site. The pressures at any one site changing linearly with change in  $G_x$ , becoming more negative when the site was superior and more positive when the site was dependent in the thorax. The difference in pressure between the dorsal and ventral sites changed from +80 cm  $H_2O$  at  $-6 G_x$  to  $-60$  cm  $H_2O$  at  $+6 G_x$ , an average gradient of 12 cm  $H_2O$  per unit  $G_x$  change. As indicated in the right panel, the vertical distance between ventral and dorsal recording sites was about 15 cm, so that there was an approx. 1-cm- $H_2O$  pressure increase at any site of the pleural space with a unit increase of  $G_x$ . This 1:1 relationship indicates that pressure in the intrapleural space under these conditions behaves similarly to a hydrostatic system. Esophageal pressure changes in much the same manner with  $G_x$  as does the intrapleural pressure at similar vertical heights in the thorax.

(Chimpanzees, Sernylan-Pentobarbital Anesthesia)  
Average and Range of Values

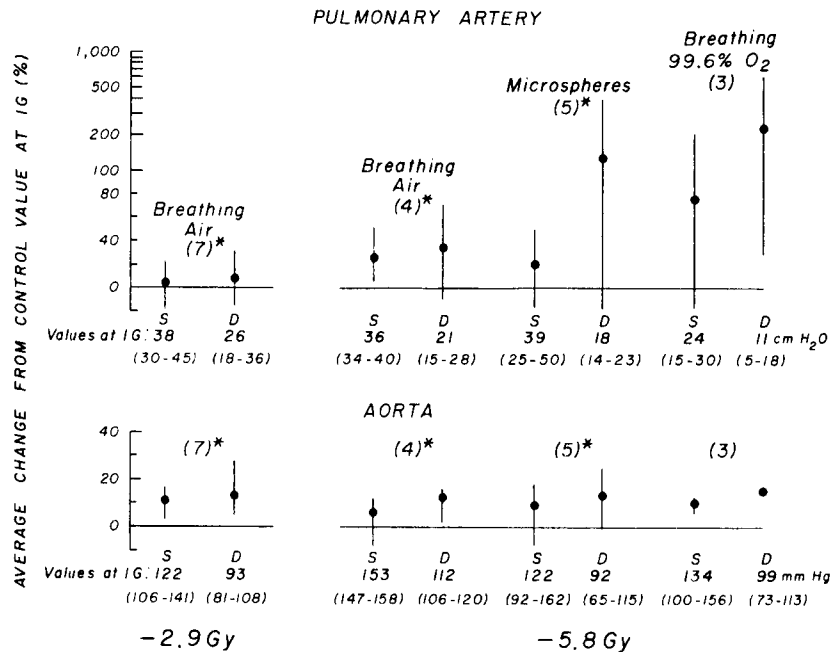


Figure 35.— Changes in systolic and diastolic systemic and pulmonary arterial pressures during acceleration of chimpanzees in the right lateral position. The numbers in parentheses within each plot denote the number of chimpanzees studied under each condition, as shown. The asterisk refers to intermittent positive-pressure breathing used in some of the experiments. The average and the range of values determined at 1 g just prior to the exposures to acceleration are given below each plot.

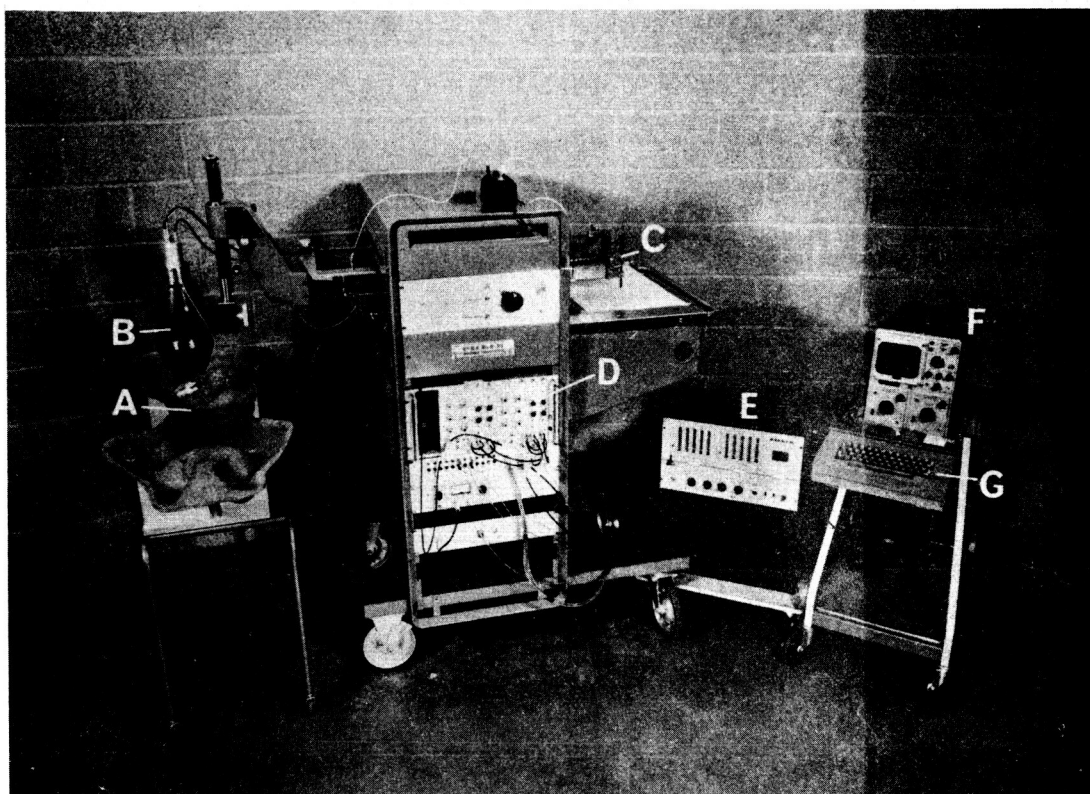


Figure 36.— Computer-controlled Magna V scanner assembly (Picker). A, half-body molded cast to maintain body position of chimpanzee constant during scanning procedure; B, collimated sodium iodide scintillation detector; C, writing arm; D, electronic assemblies for detection and positioning components of scintiscanner; E, two-channel counting assembly, one of two required; F, storage oscilloscope for computer output display at remote computer station; and G, keyboard for remote computer interrupt, program selection, and entry of auxiliary alphanumeric data prior to online processing of data from scanning assembly.

(♀ CHIMPANZEE 39 kg. SERNYLAN-PENTOBARBITAL ANESTHESIA)

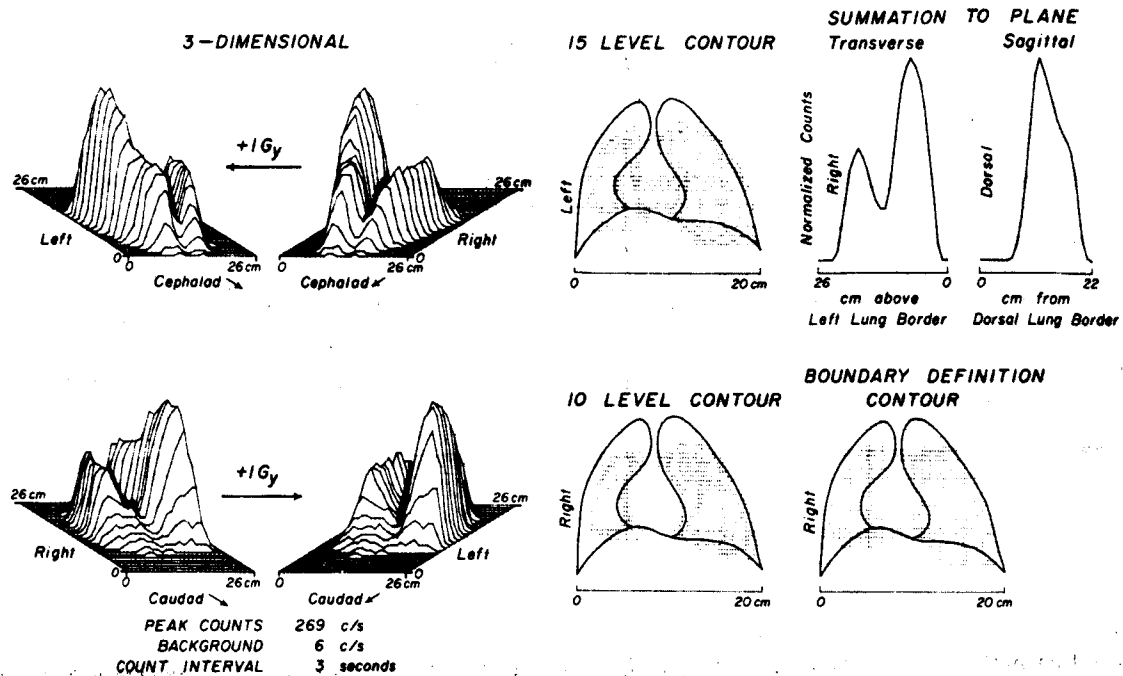


Figure 37.— Computer-generated displays of radiation levels recorded during scintiscan of the ventral surface of the thorax of female chimpanzee F following injection of tagged microspheres into the right ventricle when in the left lateral position.



( ♀ CHIMPANZEE 39 kg. SERNYLAN - PENTOBARBITAL ANESTHESIA )

# LEFT LATERAL POSITION

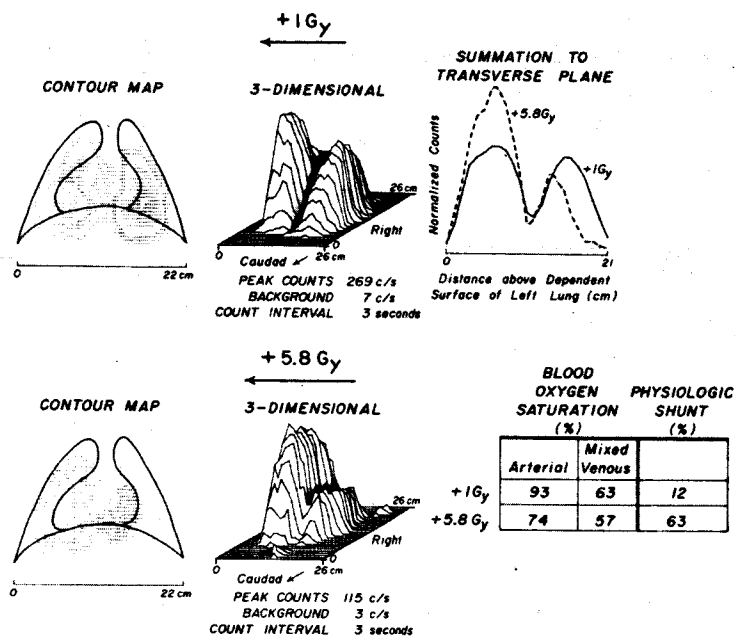


Figure 38.— Distribution of microsphere emboli in the thorax of female chimpanzee in left decubitus position at 1 G<sub>y</sub> during exposure to +5.8 G<sub>y</sub>. The tabular inserts in each figure give the oxygen saturation of systemic arterial and mixed venous (pulmonary arterial) blood and the calculated physiologic pulmonary arterial venous shunts which were present at the times of each microsphere injection when at 1 g and during the last 15 to 20 seconds of 60-sec exposures to 5.8 G<sub>y</sub>.

The physiologic pulmonary arterial-venous shunts at 1 G in this chimpanzee were small, the blood flow to the dependent, presumably nonanoxic, lung relatively large, and, at 5.8 G<sub>y</sub>, considerable displacement of blood flow to the dependent lung occurred.

*(Based on Input from Cursor Outlining of 1cm Sections of  
Lungs Embedded En Bloc in Urethane Foam)*

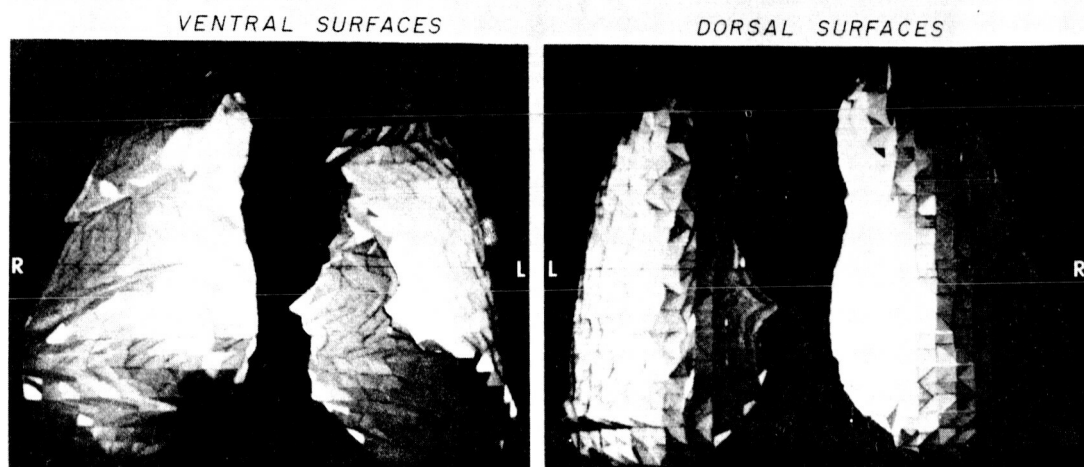


Figure 39.— Pictures of computer-generated oscilloscopic three-dimensional simulation of the ventral and dorsal surfaces of a chimpanzee lung.

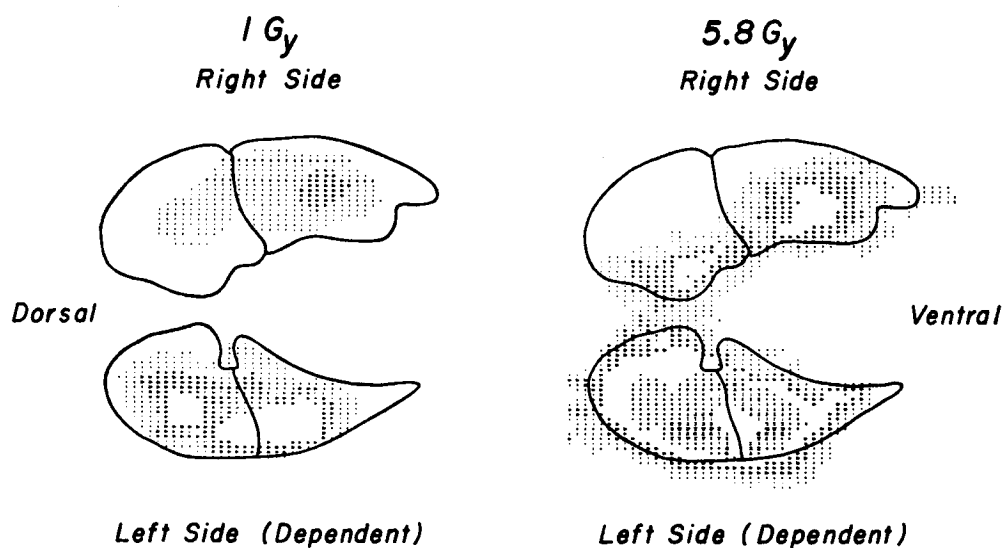


Figure 40.— Computer-printed contour plots of distribution of microspheres (blood flow) in transverse section 12 cm from the apex of the chimpanzee lungs shown in figure 39.

The hierarchy of computer-printed symbols used to designate successive count levels is as follows: blank (background level), —, A, blank, +, B, blank, C, : blank, etc. The symbol — designates the first increment of count level above background; A, the second increment; blank, the third increment; etc.

The increment in count levels for the  $^{141}\text{Ce}$ -tagged microspheres used at 1 Gy was 6 counts/sec, and for the  $^{85}\text{Sr}$  microspheres used at 5.8 Gy, 4 counts/sec.

Note the higher level of radiation (blood flow) in the dependent lung at 1 Gy and the displacement of blood flow, particularly toward the dependent border of the right (upper) lung, during the exposure to 5.8 Gy.

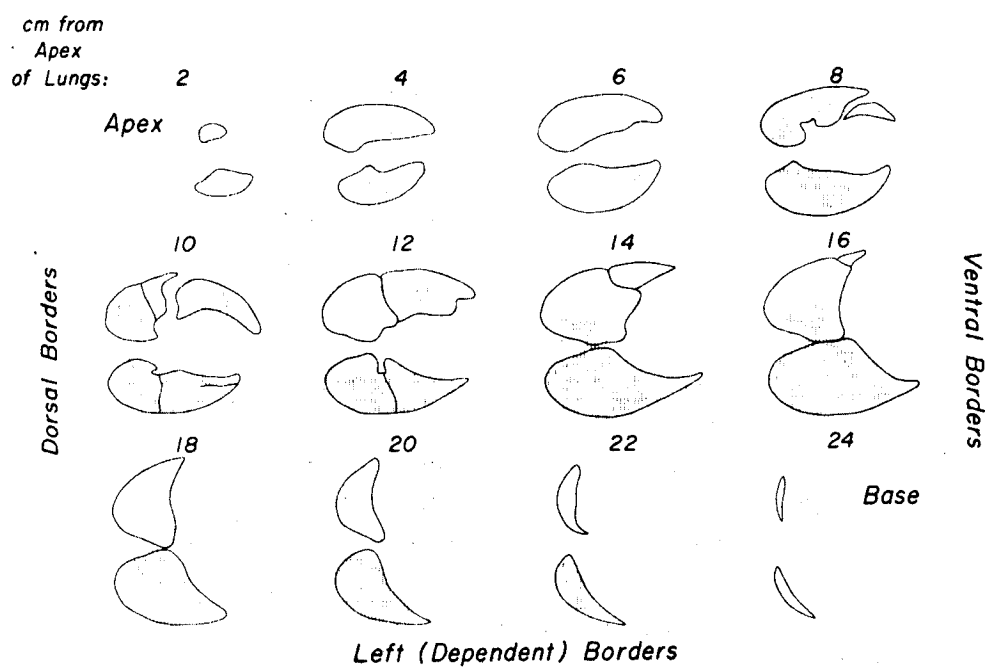


Figure 41.— Computer-generated contour plots of distribution of radioactive microspheres (blood flow) in 2-cm-thick transverse sections of the chimpanzee lungs shown in figure 39.

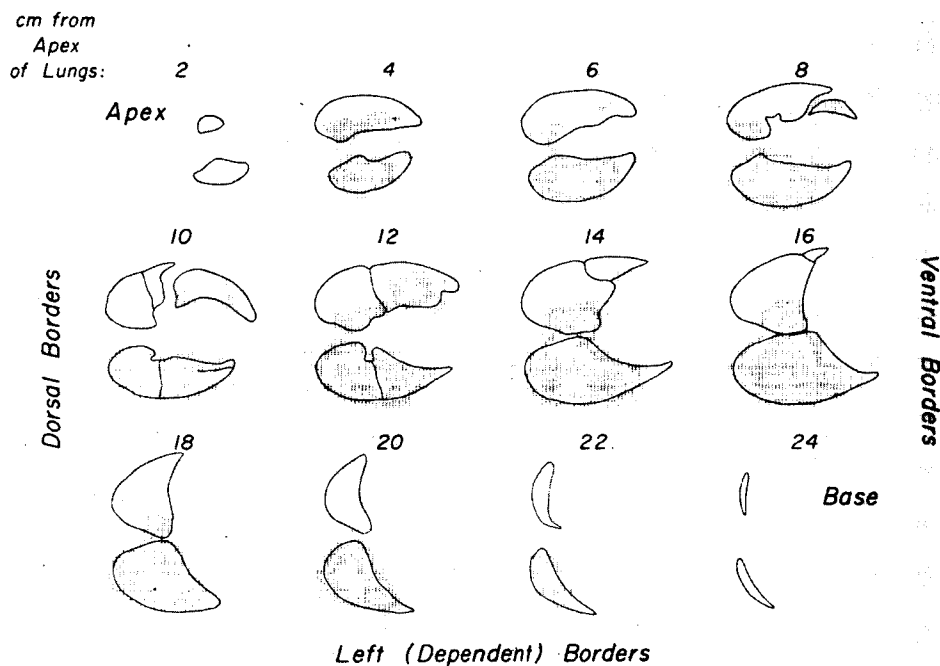


Figure 42.— (a) Distribution of microspheres tagged with  $^{141}\text{Ce}$  injected into the right ventricular outflow tract while the chimpanzee was in the left lateral position at  $1\text{ Gy}$  under Sernylan-sodium pentobarbital anesthesia.

(b) Distribution of microspheres tagged with  $^{85}\text{Sr}$  injected into the right ventricle about 15 min later, 50 sec after the onset of an exposure to  $5.8\text{ Gy}$  in the left lateral position. The  $\gamma$  radiations originating from the two isotopes were distinguished by pulse-height analysis. Note the displacement of the microspheres toward the dependent borders of both lungs, which occurred during the exposure to  $5.8\text{ Gy}$ . This effect can be seen more clearly in the closeup of the scintiscan results obtained from the cross section located 12 cm from the apex of the lungs shown in figure 40.

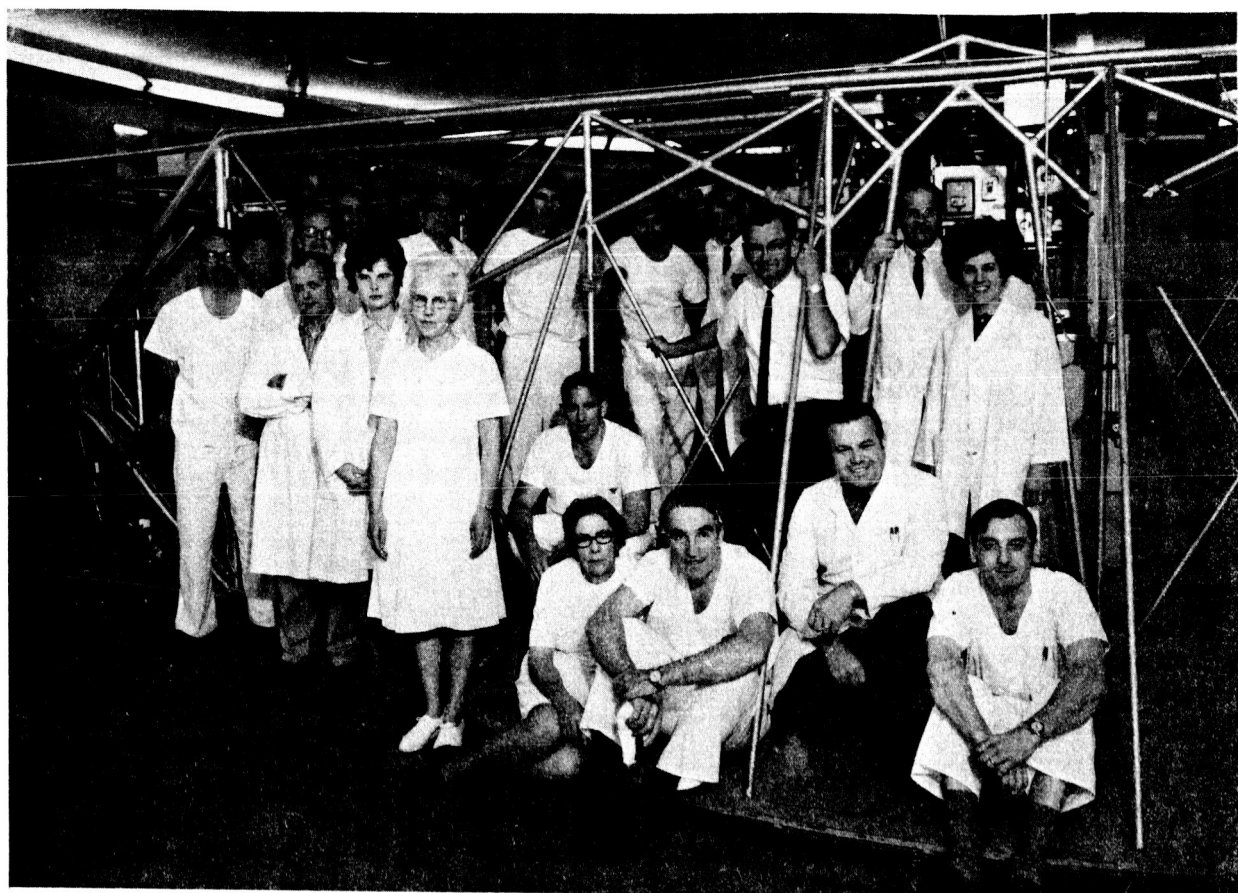


Figure 43.— Portion of team of people involved in the centrifuge experiments in 1968.

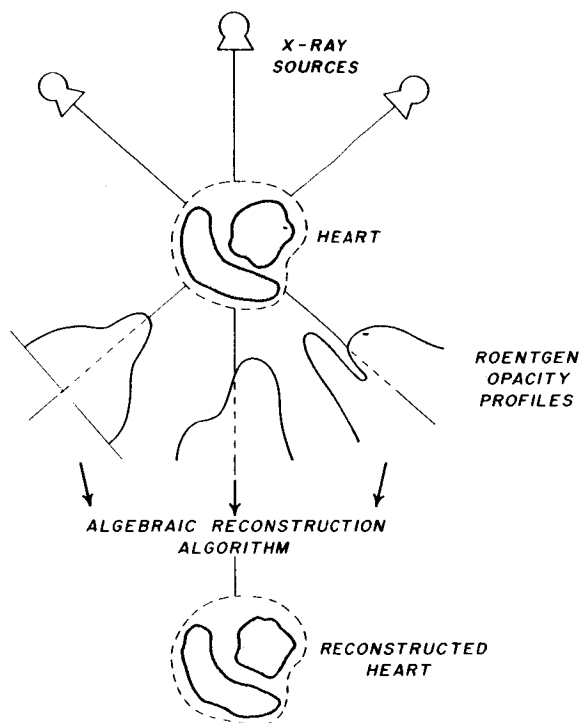


Figure 44.— Diagram of technique for reconstructing a cross section of the heart from multiplanar video roentgenograms. The dashed line represents the epicardial, and the thick solid lines the endocardial, surfaces of the right and left ventricles. The divergent beam of X-rays passing through the heart is detected by an image-intensifier and video camera and recorded on videotape. Multiplanar roentgen videograms are obtained by either rotating the heart or the X-ray system about the longitudinal axis of the heart. Roentgen opacity profiles are obtained by analog-to-digital conversion and logarithmic transformation of the varying voltages (intensities) at 1,000 points across each video line for each of the 50 to 100 horizontal sweeps (lines) of the video scanning beam which traversed the image of the heart and for each of at least 10 angles of view covering a range of  $180^\circ$ . The spatial distribution of roentgen opacities over the entire anatomic extent of the ventricles is computed from these digitized roentgen density profiles by a CDC 3500 computer using an algebraic reconstruction algorithm. The three-dimensional shape and dimensions of the entire epicardial and endocardial surfaces of the heart can be measured from the resulting images up to 60 times/sec throughout individual cardiac cycles, if desired.

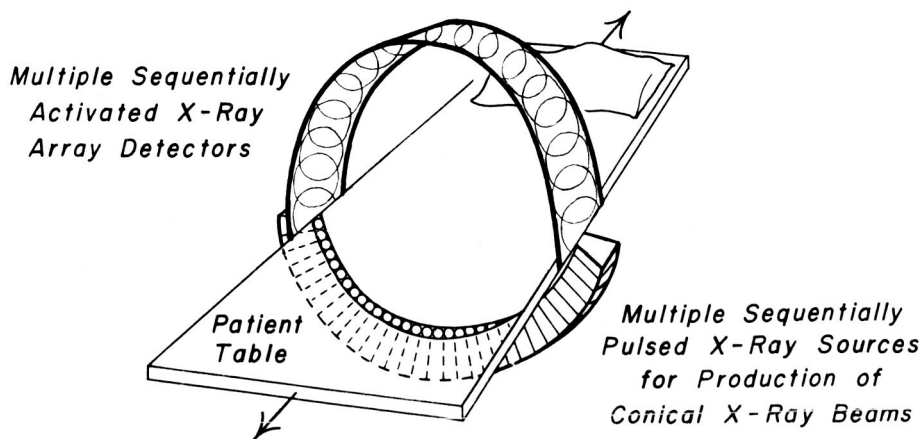


Figure 45.— Diagrammatic outline of proposed clinical dynamic spatial reconstructor. About thirty X-ray sources are arranged along a semicircle, 57 cm radius, below the patient (on horizontal movable table) and a 30 cm wide fluorescent screen is bent along an opposing semicircle of 58-cm radius. The X-ray sources are pulsed for 0.35 msec in sequence within a 10-msec period and the roentgen projection images recorded with video camera/ image intensifier assemblies mounted behind the fluorescent screen. A volume about 23 cm in diameter (i.e., portion of chest incorporating entire heart) can be reconstructed from one exposure sequence and repeated 60 times/sec.

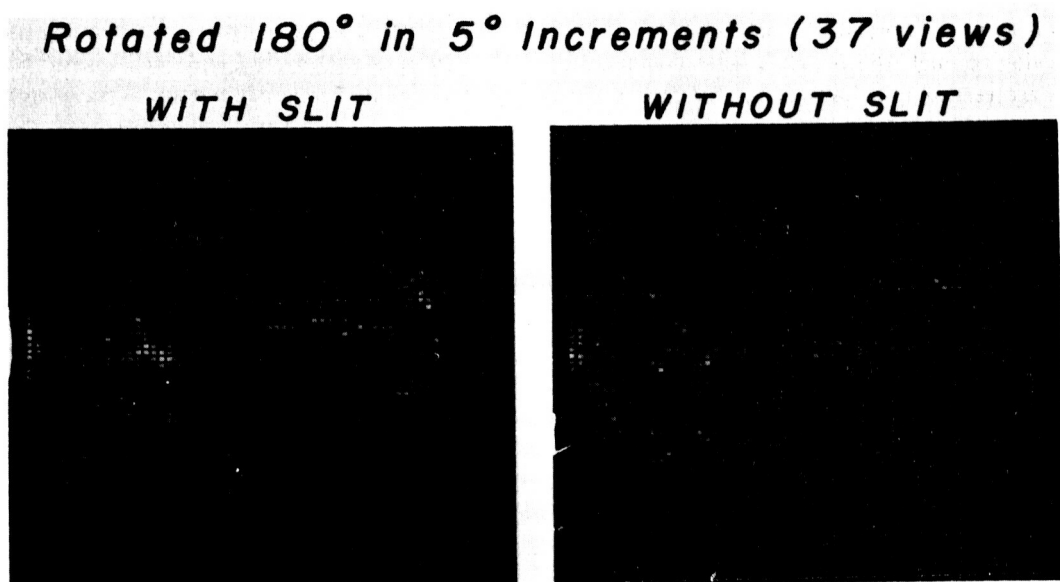


Figure 46.— Computer-generated display of cross section reconstruction of dog's thorax based on 37 equispaced multiplanar views covering a range of  $180^\circ$ . Each view was recorded at 60 fields/sec, while the dead dog was rotated about his head-to-tail axis, which was perpendicular to the central axis of the X-ray beam. Note the slightly poorer resolution in the right panel. This is the result of degradation of the multiplanar images caused by X-ray scatter, as well as scatter within the image-intensifier tube, when the recordings were made without colimating slits.



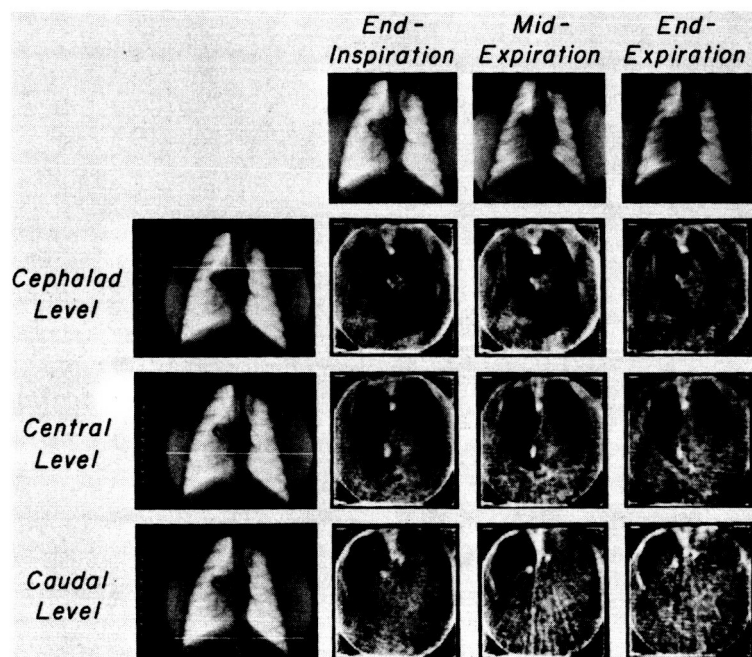


Figure 47.— Reconstructed thoracic cross sections of the intact lungs and heart of a living dog supported in the head-up position in a computer-controlled, rotatable, water-immersion respirator. Cross sections were reconstructed from 35 thoracic videoroentgenograms recorded sequentially at equiangular increments during rotation of the dog through  $183.6^\circ$ . Heart rate and respiration were computer-controlled and synchronized with rotation and image recording to provide sets of 60/sec videoroentgenograms recorded throughout the cardiac and respiratory cycles when the dog was stationary in each of the 35 positions included in the incremental rotational sequence.

Top row is a temporal sequence, from left to right, of three thoracic videoroentgenograms from the same angle of view (approximately a posterior-anterior projection; left side of dog is on left side of roentgenogram) recorded at the end-inspiratory, midexpiratory, and end-expiratory phases of the respiratory cycle, respectively, at which times the reconstructed cross sections in each column were obtained. The left column is a sequence of thoracic videoroentgenograms recorded from the same angle of view at end-inspiration with a brightened horizontal line superposed on each roentgenogram to indicate the three cross-section levels of the chest in cephalad-to-caudad (top-to-bottom spatial) sequence at which the cross-section reconstructions in each row were obtained. Horizontal bands at left margin are amplitude-modulated recordings of cardiac and respiratory pressures, pacing pulses, and other variables obtained synchronously with video image information.

The rows and columns of reconstructed thoracic cross sections show the anatomic configuration of the lungs and heart at these three different anatomic levels (top-to-bottom) and three different phases of the respiratory cycle (left-to-right), respectively. Dorsal surface of dog is at top, and left side is at right of each cross section. Note that the margins of the lungs and epicardial surfaces of the heart have been reproduced with reasonable fidelity. The bright, X-ray-dense, white spots within the thorax are roentgen-opaque catheters in the esophagus, heart, and inferior vena cava. The striking decrease in the cross section areas of the lungs during expiration is evident at the three cephalo-to-caudad cross-section levels of the chest included in this montage. The epicardial surfaces of the heart and the catheter in the right atrium, visualized in the upper and middle cross-section levels, are displaced by the dome of the diaphragm in the basal cross sections. The roentgen-opaque catheters in the inferior vena cava and esophagus are also visualized in the basal cross sections as the white spots in the middorsal region of the thorax. The cephalad movement of the diaphragm completely displaces the diaphragmatic region of the left lung from the caudad cross-section level of the thorax at end-expiration (bottom right panel).

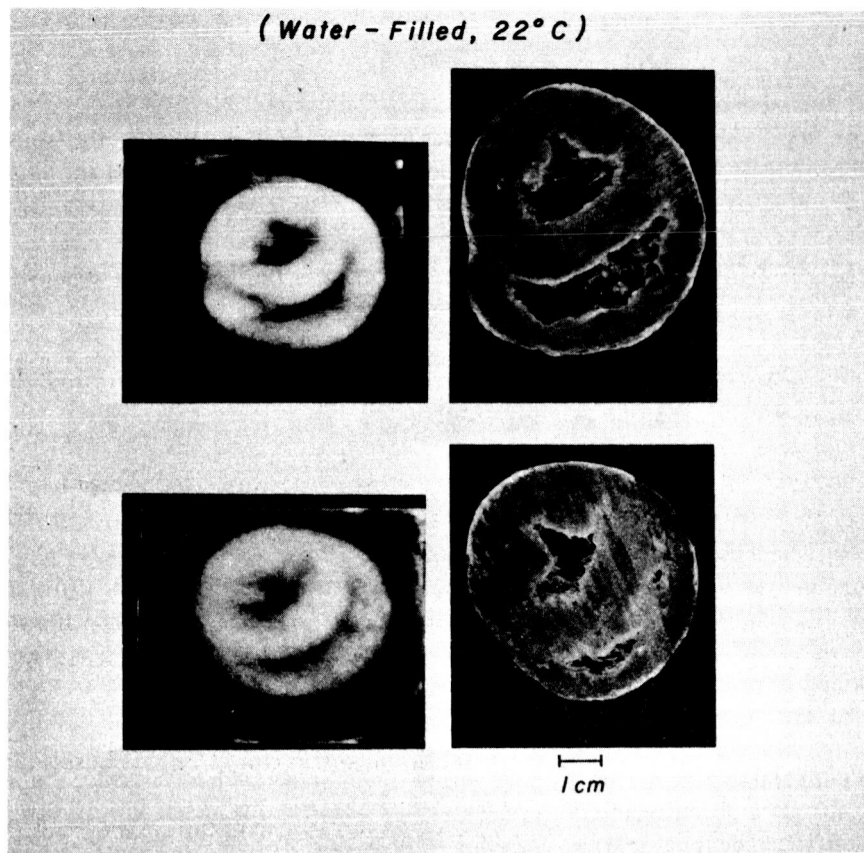


Figure 48.— Reconstructions of relative propagation delays of pulses of ultrasound within canine heart (left) compared to photographs of sections through corresponding levels (right). Diametrically opposing transducers were rectilinearly scanned on either side of the tissue in the plane to be reconstructed. Pulses were propagated through the tissue at each of 256 equally spaced points along the 12-cm scan, and were digitized with a magnitude resolution of 8 bits and a temporal resolution of  $\pm 10$  nsec. Resulting propagation delay profile was used to reconstruct relative propagation delays within each of the 64 by 64 arrays of pixels making up the image. Papillary, epicardial, and endocardial surfaces are represented with good fidelity (refs. 61 and 62).

# BIORHYTHMS AND SPACE EXPERIMENTS WITH NONHUMAN PRIMATES

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## INTRODUCTION

Biorhythms and homeostasis form the backbone of man's ability to function and survive in unusual environments. Whenever man is exposed to a new environment, he responds by making physiological adjustments that involve his health and his ability to function. This has applied to man's exposure to spaceflight and weightlessness.

The research that we have been conducting in primates and other species has been designed to answer the following series of very specific questions as they relate to man in space.

1. What is the physiological baseline? Is it constant or does it fluctuate? Does it fluctuate within a certain range and with a recurring frequency?
2. What do these fluctuations mean to various functions and responses? What are the implications to performance, to provocative tests, sensitivity to infection, radiation, drugs, or stresses?
3. What are the consequences of an altered baseline on work and performance, on emotional stability, on biomedical evaluation of man in space, on his ability to cope with the unexpected, on his susceptibility to infection, radiation, toxicity, etc.?
4. What factors in this environment or operational setup can alter this baseline?
5. If the consequences are detrimental, how can we control some factors in this environment to minimize the change? What is the effect of weightlessness alone? How do we design a study to really evaluate the effects of weightlessness on any particular system if our baseline is changing for other reasons?
6. How can we accelerate man's adjustment to the spaceflight environment – not just to weightlessness but to all the other variables that are inherent to spaceflight and that we cannot eliminate, e.g., confinement, interaction with others in craft or on ground-mission-related work and stresses?

## THE PHYSIOLOGICAL BASELINE

All physiological and psychological functions fluctuate about a mean level with circadian frequency and, hence, form the baseline of all physiological and psychological events. Figure 1 shows the baseline variation in body temperature of a *Cebus albifrons* showing a 24-hr rhythm ranging from 36.2° to 37.7° C about a mean daily temperature of 37.1° C. The normalcy and consistency of this rhythmic change in baseline are maintained by action of various environmental

events. This baseline can be altered in two directions, either by changing the *amplitude* or level or by lengthening or shortening the *periodicity* or frequency of the occurrence of the oscillations. Although the amplitude of the biologic processes may be decreased or increased fairly readily, the 24-hr period and even the phase or the time at which a particular parameter peaks or is lowest are much more resistant to change. It is also easier to lengthen the period than to shorten it.

## EFFECT OF BASELINE ON RESPONSIVENESS

During the last 20 years, it has been amply demonstrated that the time of day has a very dramatic effect on the toxicity and effectiveness of drugs (refs. 1–3), on the susceptibility to radiation and infection (ref. 4), on the response to stress (refs. 5, 6), on performance and alertness (ref. 7), and a host of other functions and provocative stimuli. Figures 2 and 3 show this characteristic effect for the toxicity of caffeine and methadone, respectively, in mice over a 24-hr period. A similar rhythmic variation in man's ability to perform the simple task of flying an airplane simulator also exists and bears a close relationship to his body temperature (BT) rhythm. More errors are made when the test is administered at the time that BT reaches a minimum and the least errors when BT is highest.

## THE CONSEQUENCES OF CHANGING THE RHYTHMIC BASELINE

There are essentially three ways in which altering the rhythmic physiological baseline relates to spaceflight.

1. Biomedical evaluation or sampling time. If the frequency or period length or time at which the peak level of a certain parameter has occurred is changing, then comparing data obtained at the same time of day during a mission will give erroneous results. This is true whether it be in the biomedical evaluation of man or in the interpretation of results from an animal flight experiment. Figure 4 illustrates how a wrong conclusion could be drawn regarding the effects of bedrest on man's heart rate (HR). If HR's were measured daily at 1500 hours during bedrest, it could be concluded that bedrest results in a slowing of the HR, whereas if they were measured at 0300 hours, it could be concluded that bedrest resulted in tachycardia. Actually, the mean daily HR is not changing during this time, but the rhythmic fluctuation in HR is shifting so that the peak now occurs 1 hr later.

2. Function and performance. Similarly, if, instead of heart rates, the rhythm in performance of work or alertness were shifting or changing and a certain task were to be performed at a fixed time each day, then the quality of the job would vary greatly. This could involve anything from carrying out a simple task, to EVA, or landing the craft.

3. Development of biomedical problems as a result of desynchronization. Under normal conditions, there is a delicate relationship of one physiological rhythm to another, which can be illustrated schematically in figure 5. As an example, the simple reaction of substrate + enzyme  $\rightleftharpoons$  product follows a distinct rhythmic pattern. A rise in substrate availability is necessary and precedes increased enzyme activity which results in increasing levels of the product.

Thus, a *synchrony* is essential among the first two rhythms for the reaction to move forward. If synchrony is disturbed for any reason, then it is obvious that the reaction cannot proceed. An awareness of daily physiological rhythm balance as synchrony is necessary because "baseline" or "control" values may vary markedly at different times of the day. More important is an understanding of the phase relationships and the stability of these daily physiological rhythms to various provocative stimuli or stress. All physiological rhythms in the body are in synchrony with each other and with the environment, and disturbances of this internal synchrony can have serious consequences. It is now being established that several disease states may be the result of such internal desynchronization (E. Weitzmann, personal communication). The susceptibility to toxic substances increases (ref. 3) and emotional stability and the ability to cope deteriorate (ref. 8). Performance also deteriorates. Figure 6 shows the results of a recent study where we measured performance in men kept first in 16 hr light-8 hr dark (16L:8D) regulated photoperiods, then in constant light at 15 fc, and finally back in 16L:8D. It was found that when physiological rhythms were not synchronized with the environment but were freerunning (as in 24L:0D), performance did not deteriorate as long as internal synchrony was maintained; whereas performance greatly deteriorated during the recovery phase when the photoperiod was again regulated but internal synchrony was disturbed.

## ENVIRONMENTAL FACTORS AFFECTING RHYTHMIC BASELINE

The literature of biology is replete with elegant studies of rhythms in lower animals and plants which establish that the primary factor controlling circadian rhythms is light, particularly the light-dark cycle in the environment, or the photoperiod. Various investigators have postulated factors that are of secondary significance as *zeitgebers* or synchronizers in maintaining the circadian period. These include, in order of priority, temperature, atmospheric pressure and composition, electromagnetic radiation (excluding visible light), magnetic fields, kinetics (e.g., linear and angular acceleration), vibration and acoustic noise, social interaction, and feeding and food composition. However, there are considerably fewer studies about the biorhythmic regulation of subhuman primates (refs. 9, 10), but it has become apparent that day-active subhuman primates and man differ considerably from other species with respect to the relative importance of various factors that regulate rhythms and rhythm synchrony. Figure 7 shows that data from man and cebus monkeys maintained under similar conditions are essentially indistinguishable. They also appear identical in their response to altered photoperiods (fig. 8).

In man, although light is also important, other factors such as social interaction (ref. 11) and posture (refs. 12, 13) may override it. Subhuman primates appear to be more like man than other animals in this respect (refs. 14, 15). Thus, it would be expected that in weightlessness, removal of the normal alternating posture cues would result in rhythmic baseline shifts and general instability of rhythms, as are seen in man in bedrest. Unfortunately, the importance of the concept of measuring continuously some parameter as an internal timing marker in the biomedical evaluation of man in flight has not been realized. As a result no such information on the effects of spaceflight exists. Preflight and postflight measurements in the Skylab series (ref. 16) and intermittent, sporadic heart rate measurements during Apollo flights are suggestive of a shifting baseline. Similarly suggestive are the findings from the Biosatellite *Macaca nemestrina*, where body temperature and other parameters were analyzed for changes in rhythmicity (fig. 9) and were shown to be freerunning (ref. 17). However, can one really attribute these changes in this or in any proposed

subhuman primate flight experiment to weightlessness alone? What other factors may have contributed to these findings? It is possible that restraint, surgical stress, dehydration, space sickness, catheterization, anticoagulants, or other variables could have contributed to these changes.

It has been shown by several investigators that stressful conditions commonly used or inherent to the use of subhuman primates in experimentation such as chairing or the use of other restraining devices (refs. 18, 19), isolation (ref. 20), surgical or sampling procedures (ref. 21), or subjection to specific food or water deprivation or reward regimens (refs. 8, 22) often used in behavioral testing are not only stressful, as indicated by activation of the pituitary-adrenal system, but also disturb the stability of the rhythmic baseline and circadian synchrony as a whole. Here again subhuman primates are different from lower vertebrates (refs. 8, 23, 24) and appear to be particularly sensitive to stress, showing behavioral abnormality and complete desynchronization of various rhythms, particularly in multiple-stress situations. Stroebel (ref. 8) illustrated this point very well. Rhesus monkeys were kept in a regulated 12L:12D environment and learned behavioral discrimination tasks. The temperature of the animal's isolation booth was then raised to an uncomfortable level. The monkeys learned that by pressing an extended left-hand lever a gust of cool air was generated. This resulted in the monkeys pulling this lever almost continuously and indiscriminately. He then superimposed behavioral stress on this situation by retracting the lever so that it could be seen but not held. This resulted in severe consequences, and two distinct groups emerged. In the one group, temperature rhythms lost their circadian frequency and became freerunning in spite of the well-regulated photoperiod (fig. 10). The animals developed ulcers and responded adequately but inefficiently on their behavioral tests. In the other group, temperature rhythms also lost their circadian frequency, becoming mostly 48-hr rhythms. The monkeys showed lassitude and weakness, their fur became poorly groomed, and they performed unpredictably, if at all on the behavioral tests. Whereas the first group recovered on reextending the lever, the second group never recovered. This example serves to illustrate that stress is one of the factors that can drastically disturb the circadian rhythmicity of the physiological baseline and override the strong regulating influence of light as the synchronizer. It also points out some of the physical, pathological, and behavioral consequences of disrupting circadian synchrony.

The situation described in Stroebel's work is not extreme, and similar multiple-stress situations can be expected to be built into many a subhuman primate flight experiment. These could include restraint, catheterization, blood sampling, behavioral tasks, food and water availability that depends on the performance of these tasks, or some other contingency. If these are coupled to isolation, confinement, space sickness, dehydration, low light intensity because of power limitations, disturbances in sleep and motor coordination, and weightlessness, it would not be surprising if the circadian baseline would be disturbed.

### WHAT CAN BE DONE ABOUT IT?

The simplest thing that can be done is to go into the design of a flight experiment with an awareness of what circadian rhythms are, what factors affect them most and, since they form the physiological baseline, with an awareness that anything that changes the rhythms impacts on all biomedical flight experiments, not just those designed to investigate circadian rhythms. Secondly, all primate flight experiments should include the continuous monitoring of some physiological

parameter as an index of internal time. Those experimental factors that are known to affect rhythms should be eliminated, minimized, or suitably controlled (table 1) for each flight experiment.

Our research program in this area has undertaken the systematic study of the relative contribution of various flight-associated variables affecting rhythms. Determining the optimal requirements for maintaining normal rhythmicity applies not only to subhuman flight experiments but also to man in space because regulation of their rhythms are so similar. Our primary aim is to develop operational standards and controls for those flight-associated variables such as photoperiod, light intensity, light spectrum, etc., that can be corrected. Secondly, we would like to obtain suitable and specific solutions for some of these variables. For instance, we are presently investigating the possibility of allowing an animal to self-select his photoperiod. This is of special significance since this is one of the obvious options available to man in spaceflight. Finally, we need to quantitate the effect of those flight-associated variables that cannot be avoided, one of which, of course, is weightlessness.

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**TABLE 1.— EXPERIMENTAL FACTORS AFFECTING  
SPACEFLIGHT EXPERIMENTS**

<u>EXPERIMENTAL VARIABLES</u>	<u>FLIGHT ORIENTED VARIABLES</u>
RESTRAINT	PHOTO PERIOD
SURGICAL IMPLANTS	LIGHT-INTENSITY
CATHETERIZATION	LIGHT SPECTRUM
BEHAVIORAL TASKS	ACCELERATION
FEEDING/WATERING SCHEDULES	TEMPERATURE
	ATMOSPHERE
	FEEDING/WATERING SCHEDULES
	FOOD COMPOSITION
	NAUSEA/VOMITTING
	DEHYDRATION
	WEIGHTLESSNESS

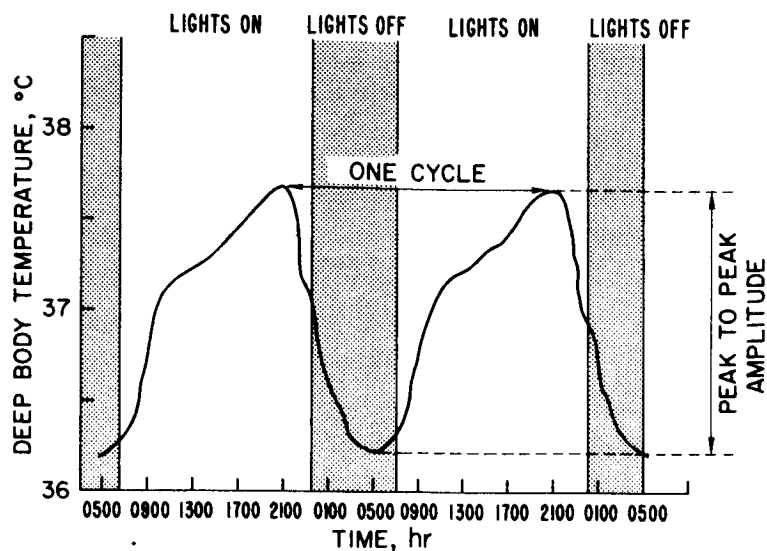


Figure 1.— The physiological baseline variation in body temperature of a *Cebus albifrons* showing a 24-hr rhythm, ranging from 36.2° to 37.7° C about a mean daily temperature of 37.1° C.

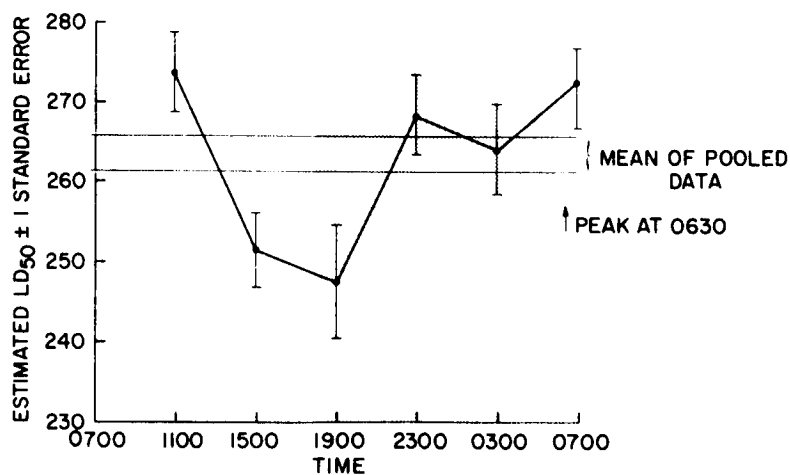


Figure 2.— Circadian rhythm in toxicity of caffeine in mice. Expressed as LD<sub>50</sub> (mg/100 g body weight  $\pm$  SE)

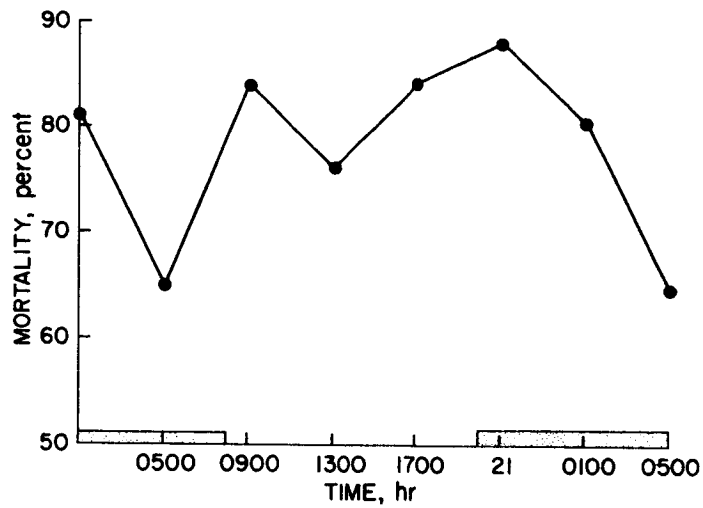


Figure 3.— Circadian rhythm in toxicity of methadone.

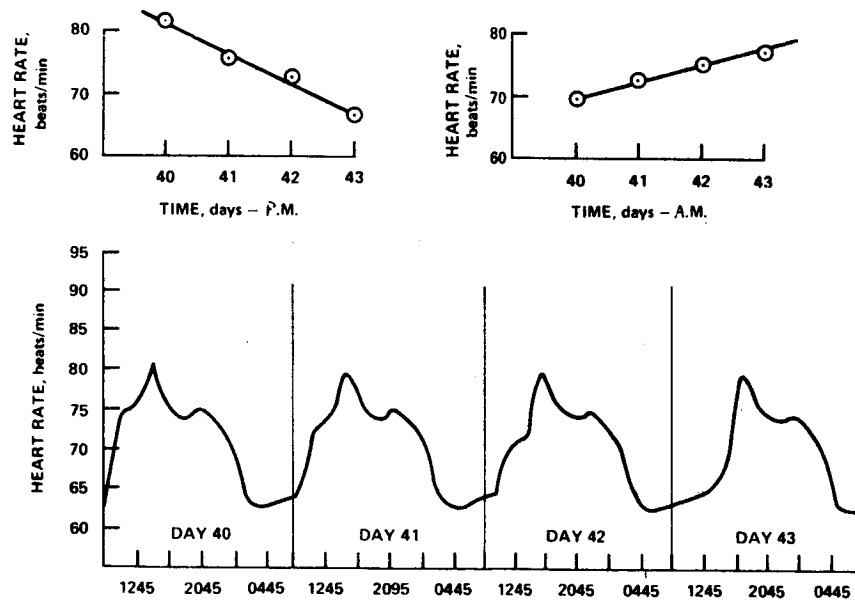


Figure 4.— Effect of bedrest on man's heart rate.

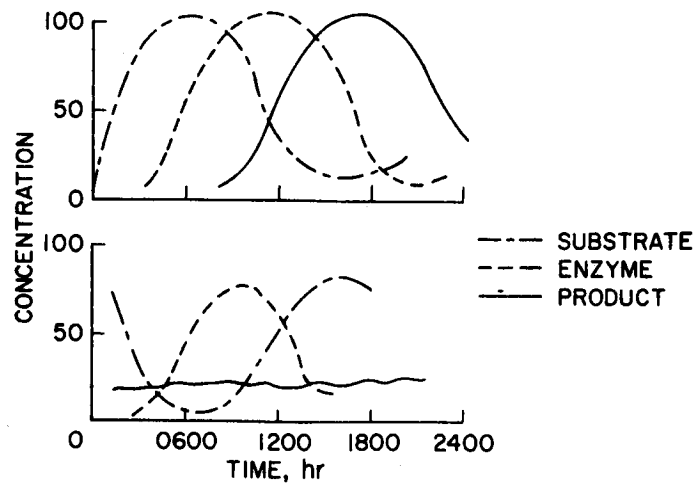


Figure 5.— Schematic representation of the importance of synchrony of various rhythms to physiological processes.

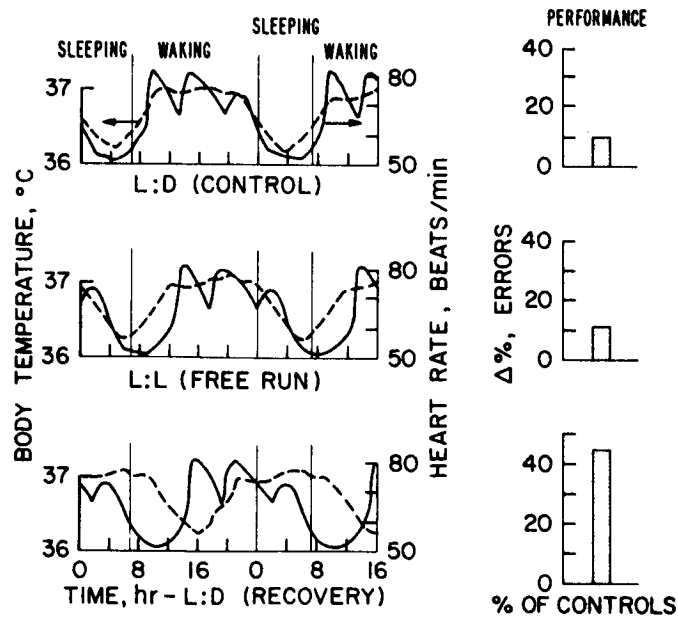


Figure 6.— Effect of internal synchrony on performance in man.

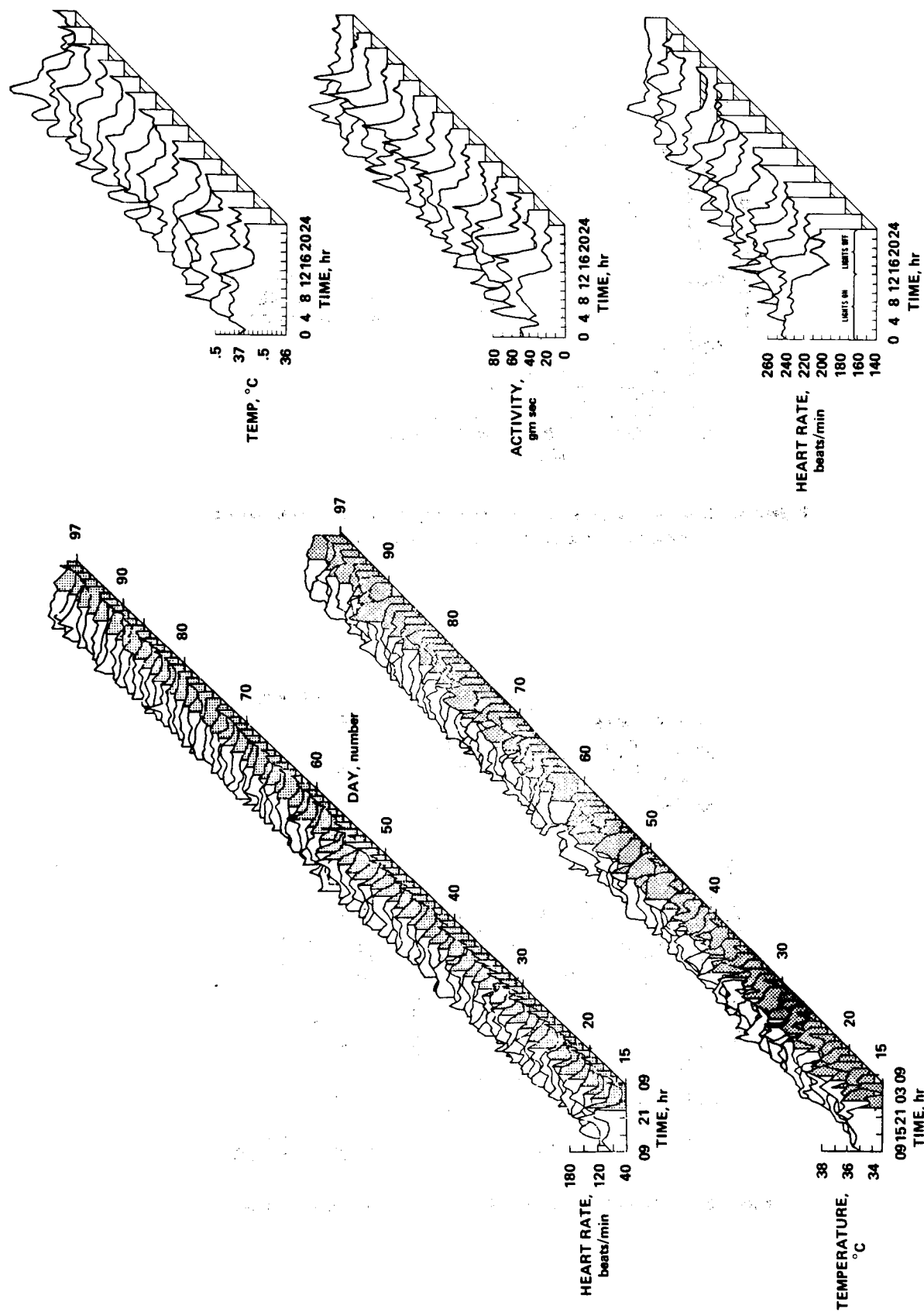


Figure 7.— Comparison of human and subhuman primate data collected on a continuous basis.

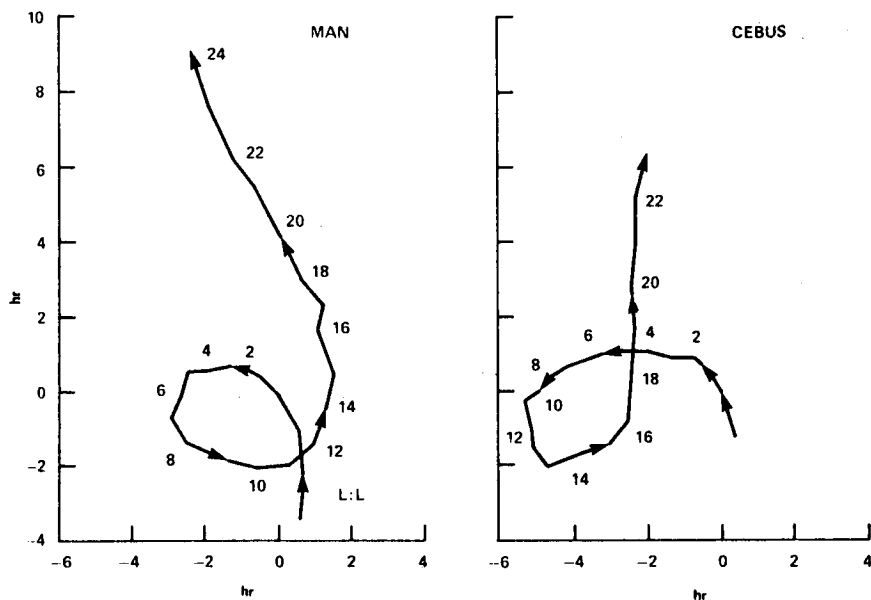


Figure 8.— Comparison of the body temperature rhythm response to a change in photoperiod in human and subhuman primate (summation dials).

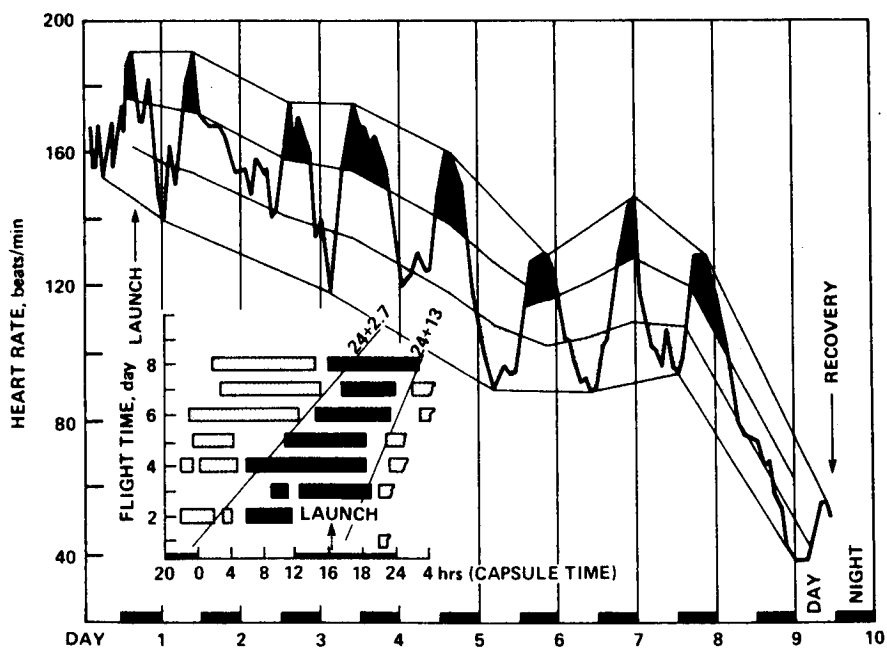


Figure 9.— Body temperature rhythms of *Macaca nemestrina* during a Biosatellite mission.

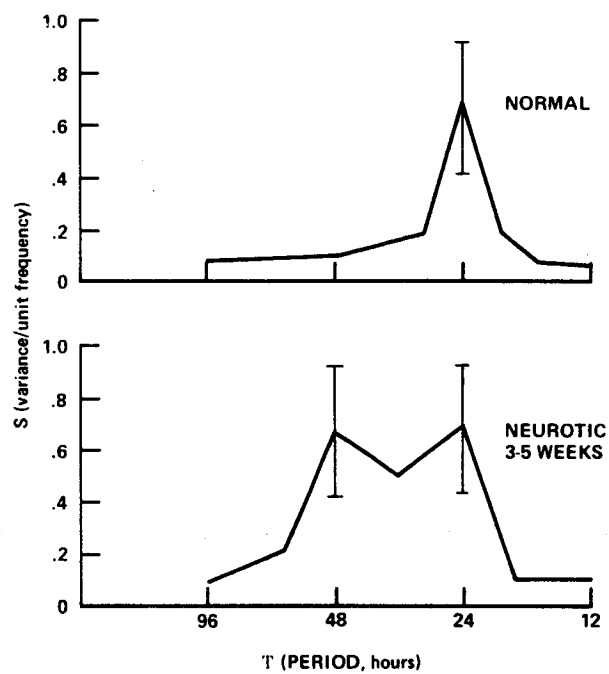


Figure 10.— Periodogram of rhesus monkeys exposed to behavioral stress.

# VESTIBULAR FUNCTIONS AND SLEEP IN SPACE EXPERIMENTS

## WITH NONHUMAN PRIMATES

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### INTRODUCTION

Research on neurophysiological effects of orbital flight has been concerned with both vestibular responses and the mechanism of the sleep-wakefulness cycle in both human and nonhuman primates. The findings of this research have led to additional efforts in ground- and air-based experiments utilizing facilities for reproducing spacecraft conditions. Two such efforts have been conducted by the Laboratory of Neurophysiology at Yerkes. These were concerned with the chronic effects of vestibular stimulation on neurophysiological aspects of sleep and with the effects of altered gravity on the vestibulo-ocular reflex to angular acceleration.

### EXPERIMENT I: VESTIBULAR EFFECTS ON SLEEP

The first set of experiments dealt with the question of how cycles of sleep and wakefulness, as measured by physiological indices of sleep (i.e., electroencephalograms (EEG) of cortical and subcortical activity, electro-oculograms (EOG), and electromyograms (EMG) of the cervical muscles), were affected in monkeys living in a rotating cage. It had been noted in earlier research with human subjects, conducted at the Naval Aerospace Medicine Institute in the Slowly Rotating Room facility, that chronic exposure to constant velocity (10 rpm) angular rotation for 12 days, a rate equivalent to that proposed for rotating space platforms, produced a marked decrement in performance in vigilance tasks and resulted in reports of chronic fatigue by crew members (ref. 1). These results were, in part, replicated by others (ref. 2). A brief report from a Russian laboratory (ref. 3) also presented evidence that sleep, as monitored electroencephalographically, could be altered in subjects exposed to prolonged, constant, rotational velocity. These findings suggested that a form of sleep deprivation might be induced by the complex and bizarre vestibular stimuli presented to the semicircular canals as the crew members made head movements of sufficient acceleration outside the primary plane of rotation, thus accounting for the decrement in vigilance task performance and the fatigue syndrome reported by Graybiel, et al. (ref. 1). Presumably, little or no vestibular stimulation occurred during actual sleep while the subjects lay in a recumbent posture. Since the subjects were not monitored electrophysiologically during the periods of wakefulness, it was not determined if the decrement in vigilance might have been related to the intrusion of episodes of drowsiness during the normal period of wakefulness.

The purpose of the experiment we conducted with monkeys was to gain additional data on sleep disturbances documented by continuous recordings throughout a week of continuous rotation, with control nonrotational recordings preceding and following the period of vestibular stimulation. If sleep deprivation is produced by prolonged rotation, one might expect a rebound



recovery in sleep duration during postrotation recordings. Continuous monitoring provided data on physiological responses of the monkeys while they experienced Coriolis forces as they moved about the recording chamber. The EOG acted as an index of the effectiveness of these forces as vestibular stimuli to induce nystagmus.

## MATERIAL AND METHODS

Owl monkeys were selected as subjects both for their convenient size and for electrophysiological characteristics in their sleep patterns that resemble those found in more highly developed primates, including man. Moreover, it was felt that vestibular effects on sleep might be more pronounced in this species. Since nocturnal monkeys would be moving during the dark phase of each day, they would experience vestibulo-ocular nystagmus for longer periods, lacking the visual reference points necessary for fixation that would aid in attenuating the vestibular reflex.

We designed an apparatus that would allow continuous monitoring of the primary physiological parameters of sleep in a monkey living in a chamber rotating continuously at a constant angular velocity (see fig. 1). Recordings were made from animals with chronically implanted electrodes for monitoring EEG, the EOG of horizontal eye movements, and the EMG activity of the upper neck muscles.

The centrifuge was designed to perform like the Slowly Rotating Room at Pensacola (ref. 1) with one significant difference: the cage was mounted at a fixed angle to the horizontal calculated so that a relatively constant resultant force would act cephalocaudally on the animal as it walked about the cage. Two side walls of the cage were made of one-way screens. The center of the 37 cm X 43.75 cm X 43.75 cm (15 in. X 17-1/2 in. X 17-1/2 in.) cage was located 0.75 m (2-1/2 ft) from the center of rotation on two radially oriented parallel beams.

The electrodes were chronically implanted and soldered to miniature electrical connectors implanted on the animals' skulls. The electrical connectors were attached by a shielded cable to a set of miniature slip rings mounted to a counterweighted assembly at the top of the cage. This allowed the monkeys relative freedom of movement in all directions. The cable from the stationary portion of the slip rings was led to a set of signal conditioners. The amplified signal was transmitted through another set of slip rings to a polygraph recorder. Lighting conditions were controlled in a 12/12 hr light/dark cycle. A white-noise generator was used to mask laboratory noises that might have disturbed the sleep of the owl monkeys, which occurs primarily during the light portion of the day (ref. 4).

Continuous recordings, beginning after 1 week of adaptation, were made for 1 week prior to the beginning of rotation. The subjects adapted to the environmental conditions as demonstrated by a stable diurnal pattern of sleep and wakefulness and normal intake of food. The food bin was placed in the wall of the cage located farthest from the center of rotation. This wall also was the door that allowed access to the animal. All the subjects tended to spend most of their time facing away from the center of rotation, seated on a pedestal located opposite the food bin. Thus, when they ate during rotation, both vertical and radial movements were made, often producing sufficient Coriolis effects that elicited nystagmus (see fig. 2).

The centrifuge was operated at a constant angular velocity (10.75 rpm). The constant, resultant acceleration acting in a direction perpendicular to the cage floor was calculated at 1.0049 G. During the period of rotation, the centrifuge was decelerated once a day to a speed of less than 1 rpm, for a period of less than 5 min, in order to fill the food bin. This usually occurred at the end of the light period at about 1730 hr.

Analysis of the electrophysiological data was accomplished by a hand-scoring method that is a modification of the scoring criteria developed for assessing human sleep EEG recordings. The system used in this laboratory for scoring sleep in owl monkeys divides sleep into two stages of slow-wave sleep,  $S_I$  and  $S_{II}$ , that correspond to human EEG sleep stages I, II and III, IV, respectively, and the rest of sleep is classified as rapid eye movement or REM phase. Basically,  $S_I$  and  $S_{II}$  differ from each other in percentage of slow-frequency components.  $S_I$  sleep is that sleep stage that emerges as the animal becomes drowsy, and that usually occurs preceding awakening.  $S_{II}$  stage sleep is characterized by a virtual absence of sleep spindles and a preponderance of relatively high-voltage waves falling in a frequency band width of 1–3 Hz. During both slow-wave sleep stages, the EOG exhibits little activity except for slow, drifting, eye movements. The EMG of the neck muscles usually indicates an atonia which is characterized in these recordings by very low amplitude electrical activity.

During REM phase sleep, the neck muscles are similarly inactive except for occasional clonic muscle twitches. In contrast, during REM sleep, EEG recordings from both cortical and subcortical electrodes and the EOG exhibit activity that resembles in many respects recordings made during wakefulness. During wakefulness, the EMG is characterized by a tonic increase in activity with high-frequency and high-amplitude bursts occurring during locomotion and head movements. Each of these characteristics was used as criteria to score polygraph recordings. One-minute segments of the recordings were each classified according to that stage of sleep or wakefulness that represented at least 30 sec of that interval.

## RESULTS<sup>1</sup>

The subjects adapted well to the constantly rotating environment. There was no evidence of motion sickness. The monkeys appeared to eat and drink normally throughout the experiment. Four experiments were conducted with three owl monkeys. Statistical analyses were performed on one complete set of recordings from a single subject. The major diurnal cycle of sleep and wakefulness was maintained, i.e., the major proportion of all sleep occurred during the 12-hr light period (DL), while the recordings during the 12 hr of darkness (ND) were primarily scored as wakefulness (W).

While the lights were off, during rotation, frequent and short-lasting episodes of nystagmus were observed (fig. 2). Each beat of nystagmus was accompanied by spike discharges in the lateral geniculate nuclei and the striate cortex that correlated with the fast-phase eye movements. These potentials are most frequently observed in owl monkeys as correlates of saccadic eye movements during wakefulness and also occur with relative independence of fast eye excursions during all

<sup>1</sup> A brief abstract of these results appears in reference 5, p. 31.

phases of sleep (ref. 6). Nystagmus occurred on all days of rotation and thus showed no adaptation to the intermittent stimuli produced by head movements. There was no evidence of nystagmus during any phase of sleep. This was as expected since this species sleeps in a curled, huddled posture, and head movements are not made during sleep.

The most marked sleep alterations observed during rotation were in the selective reduction in two stages of sleep:  $S_{II}$  and REM phases. Significant decreases in  $S_{II}$  and REM sleep as a percentage of the ND phase of the day (1800–0600 hr) were observed (Mann-Whitney U,  $p < 0.008$ , see fig. 3). A similar suppression in  $S_{II}$  occurred during the DL phase (0600–1800 hr). There was a compensatory increase in both  $S_I$  phase sleep and wakefulness, although neither increased significantly above prerotational levels. There was no notable increase or rebound for either  $S_{II}$  or REM phases of sleep.

The number of episodes of  $S_{II}$  and REM was significantly fewer (Mann-Whitney U,  $p < 0.001$ ) during the ND phase of the period of rotation. Following rotation, the number of episodes of both stages during ND halves of the day increased toward prerotation amounts. A nonsignificant increase in the number of REM episodes in the DL postrotation recording periods was also observed (see fig. 4).

## SUMMARY OF RESULTS

In summary, significant specific alterations were induced in the sleep-wakefulness cycle by prolonged exposure to constant rotation. Since these effects were primarily limited to the dark phase of the day when this species is normally active and when most of the vestibular stimulation from Coriolis forces occurred, it appears that the reduction of sleep was directly related to vestibular disturbance, but that these effects were not long lasting and did not disrupt sleep during the normal period of inactivity. The exception was the overall suppression of the  $S_{II}$  phase in both nocturnal and daylight sleep periods. These findings, taken with the results of performance experiments on humans living under similar conditions, indicate that the effects of forces acting on an organism moving in a small rotating environment, such as a spinning space vehicle, though subtle, may result in significant alterations in both physiological and behavioral measures.

## EXPERIMENT II: EFFECTS OF ALTERED GRAVITY ON THE VESTIBULO-OCULAR REFLEX

The second set of experiments was concerned with a test of the interaction of linear and angular accelerations on nystagmus. Rotation of human subjects at a constant velocity around an Earth horizontal axis produced prolonged nonadapting nystagmus under Earth standard gravity conditions (refs. 7, 8). These results may be related to direct actions on both macular and semicircular canal receptors. Ampular nerve fibers in frogs alter their resting discharge frequency when the preparation is tilted (ref. 9). These findings suggest that linear accelerations may not only alter the vestibulo-ocular reflex by rotating the linear vector around the head, as in the "split" rotation experiments, but also may influence the reflex to angular acceleration when gravity is altered.

For the last 3 years, we have tested the vestibulo-ocular reflex in awake, restrained rhesus monkeys flown in parabolic trajectories that produce brief periods of reduced gravity. It was hypothesized that changes in the nystagmus reflex, when the monkeys were angularly accelerated during the portion of the parabola when linear acceleration due to gravity is lessened, would constitute additional and critical evidence for interaction of both forces on the vestibular responses. This is a brief preliminary report of the results of those experiments.

## METHODS

The test animals (rhesus monkeys) were restrained in a standard primate chair placed within a chamber that was itself mounted to the shaft of a d.c. torque motor. A head restraint device, extending from the vertical chair supports, was coupled to alignment tubes that were chronically attached surgically to the monkey's skull. The head of the subject could thus be held rigidly, with no pressure points, so that the horizontal semicircular canals were positioned nearly parallel to the base of the chair's mounting platform, which constituted the plane of rotation (see fig. 5). The vertical axis around which the chair rotated passed through the midline of the animal's head through the midline of the interaural line. Direct current recordings were made of eye movements through platinum-plated, silver-silver chloride ball electrodes, of approximately 1 mm diameter, that were chronically implanted in the bone ridges of the outer canthi, bilaterally, and in the supra- and infra-orbital ridges of the left eye. Thus, vertical displacements of that eye and summated (conjugate) horizontal eye movements were detected in the EOG.

Since the chamber completely shrouded the animal, a video camera was mounted beside the chair and focused on the monkey's face so that the status of the animal could be checked when the light within the chamber was on. In addition to the EOG, two force measures were obtained through accelerometers mounted in the axis of rotation directly over the center of the animal's head and beside one of the vertical chair supports, oriented in a radial direction. The vertical accelerometer measured alterations in the gravity vector; the radial accelerometer detected a resultant of angular acceleration when the chair was rotated. Chair rotation was controlled by a velocity servo system that regulated the d.c. torque motor. The system could be operated in either manual or automatic modes.

A test profile for angular acceleration was chosen that would be of sufficient strength to evoke a reliable response in less than 15 sec in a ground-based, 1-G control test. This limitation was based on the shortest period for zero G expected during parabolas flown by the test aircraft, a modified KC-135A. The velocity curve of a typical angular rotation test described a symmetrical trapezoid representing 5 sec of constant angular acceleration, immediately followed by 3 sec of zero acceleration and constant rotational velocity that is followed by 5 sec of constant deceleration equal in magnitude to the acceleration phase.

During the flight experiments, the test profile was initiated by the investigator after the pilot signaled that the trajectory was stabilized at the desired gravity level. A schematic illustration of the parabola for the zero-G trajectory is represented in figure 6. The actual profile of gravity during a typical zero-G maneuver was characterized by fairly abrupt transitions from increased to reduced gravity (see fig. 7). It was also possible to alter the flight parameters to achieve partial Earth gravity levels. This capability was used for tests at  $1/3$  (Martian G) and  $1/6$  (Lunar G) Earth standard

gravities. A small number of acceleration tests was made during 360° turn maneuvers that produced a relatively constant 2-G condition.

Three variables were investigated at each gravity level: (1) angular acceleration, (2) lighting conditions, i.e., chamber lighted or dark, and (3) direction of rotation. Since the period of angular acceleration was brief, suprathreshold accelerations were used. Relatively high accelerations were required to produce nystagmus with a short enough latency so that a sufficient number of eye movements occurred for reliable measurement of the reflex. Thus, the three acceleration levels selected for flight experiments were  $10^\circ/\text{sec}^2$ ,  $20^\circ/\text{sec}^2$ , and  $63^\circ/\text{sec}^2$ . Each test profile was used for each reduced gravity level, rotating the animal alternately clockwise and counterclockwise with the chamber lights on or off so that each combination of variables was tested at least one time during the series of flight experiments in each of two monkeys. A third monkey was tested in later flights under all conditions except for the  $10^\circ/\text{sec}^2$  and  $20^\circ/\text{sec}^2$  accelerations. This was decided on the basis of data analyses of previous experiments in which both higher variance and a marked attenuation of nystagmus occurred with repeated tests at the two lower levels of acceleration in both ground and aircraft conditions. Subsequent tests in all subjects were conducted at high acceleration ( $63^\circ/\text{sec}^2$ ). We have found that for the brief duration of the test profile this is not above physiological limits of the vestibulo-ocular reflex (see fig. 7).

## RESULTS

Three monkeys have been tested to date in over 300 parabolas. None of the animals vomited during any phase of the ground or air-based tests, although there were some indications of symptoms that have been related to motion sickness, i.e., salivation and drowsiness. Although reduced alertness can attenuate the vestibulo-ocular reflex to lower values of acceleration, all subjects were aroused by the highest angular acceleration test.

Nystagmus was quantified by several measures, e.g., beat frequency, latency of onset, duration, etc.; however, the index that was best related to the angular velocity of the chair was the velocity of the slow-phase compensatory eye movement of nystagmus. This is consistent with the psychophysical measure of the relationship between angular velocity and the eye movement reflex in human subjects (ref. 10). We were unable to calibrate our recordings in terms of the relationship between EOG signal amplitude and degrees of lateral eye displacement. Instead, the velocity of the slow phase of nystagmus was estimated by measuring the voltage of the EOG, recorded from magnetic tape onto a direct writing recorder (Honeywell Model 1858), as centimeters of deflection per unit time. This measure avoids the problems of nonlinearity in the EOG (ref. 11) and also circumvents the difficulty of verifying the reliability of eye movement calibrations based on eye-tracking operant responses.

Lighting conditions had a significant effect on the vestibulo-ocular reflex, independent of gravity conditions. The magnitude of slow-phase eye velocity was lower when the lights were on in the chamber. This finding confirmed the well-known effects of visual input on the vestibulo-ocular reflex. Alternation of clockwise and counterclockwise rotations in successive tests served to lessen adaptation. However, since there seemed, in individual subjects, to be slight differences in response related to direction of rotation, all comparisons across gravity conditions were made for the same direction.

In general terms, the plot of slow-phase velocities was similar across gravity conditions, especially during the acceleration phase of the test profile. There were no consistent or marked differences in total number of eye movements measured from the beginning of the test profile until the end of deceleration. Postrotatory nystagmus in flight tests was brief, perhaps due to attenuating effects on the reflex of increased gravity during the dive (ref. 12).

The reflex at partial gravity levels was characterized by reduced slow-phase velocities compared to responses at Earth gravity. For given lighting conditions and rotational directions, there were differences in nystagmus across repeated tests at zero-G conditions. This variance was not as marked for responses at 1/6- or 1/3-G levels. Zero-G response patterns ranged both higher and lower than nystagmus recorded at 1-G, 1/6-G, and 1/3-G levels. The data graphically illustrated in figures 8 and 9 were taken from comparable accelerations in the test sequence at each gravity level. The points of separation in response magnitude across gravity levels were generally found in the postacceleration phase of the profile, during constant rotational velocity. Although zero-G responses varied considerably during acceleration, the most consistent finding was a reduced amplitude in slow-phase eye velocity relative to 1-G response during the constant-velocity phase of the test profile. Despite the variability in response at zero-G, the data at partial gravity seem to indicate a fairly consistent suppression of nystagmus under those conditions relative to that observed under Earth gravity.

Perhaps the most surprising results were the responses to angular acceleration under hyper-grav (2 G) conditions. Three such tests have been made to date, all with the chamber lights on. These results represent the lowest slow-phase eye velocities for all test conditions (see fig. 9) for both the acceleration and constant-velocity portions of the test. There is one other report of suppression of nystagmus under hypergrav conditions (ref. 12). In that experiment, rabbits were rotated on a torsion swing during either the weightless or increased gravity portions of a parabolic flight. There was an inverse relationship between increased gravity above 1-G levels and both the amplitude and duration of rotary nystagmus. This held for the first 12 sec of increased gravity, then the vestibular response adapted and recovered slowly. In our brief experiments, the reflex was suppressed throughout continuous increased acceleration in three successive tests, each lasting 15 sec.

## SUMMARY OF RESULTS

In summary, the results of the present experiment indicate a relationship between the linear acceleration of gravity and the strength of the vestibulo-ocular reflex to angular acceleration. These tests might have been affected by the confounding of hypergravity and hypogravity components of the parabolic trajectory that preceded and followed each test. That is, the increased gravity encountered during the climb might bias the inner ear mechanisms so as to alter the response during the subsequent "weightless" portion of the parabola. Alternatively, the first few seconds of weightlessness may represent an uncertain condition for the otolith receptors. Recordings of the activity of otolith-related fiber in the Eighth nerve of frog preparations, during parabolic flight, demonstrated that the rate of discharge can increase for the first 10 sec of weightlessness, followed by a reduction in firing rate below that recorded in level flight (ref. 13). This may in part account for the variance in the vestibulo-ocular reflex for zero-G parabolas. Moreover, an adaptation in the vestibular response may have occurred with repeated testing. Both of these alternatives are difficult

to investigate in parabolic flight experiments because of confounding variables and limited time for testing. It would be interesting, therefore, to compare the present findings with data from experiments conducted under conditions of prolonged weightlessness in orbital flight.

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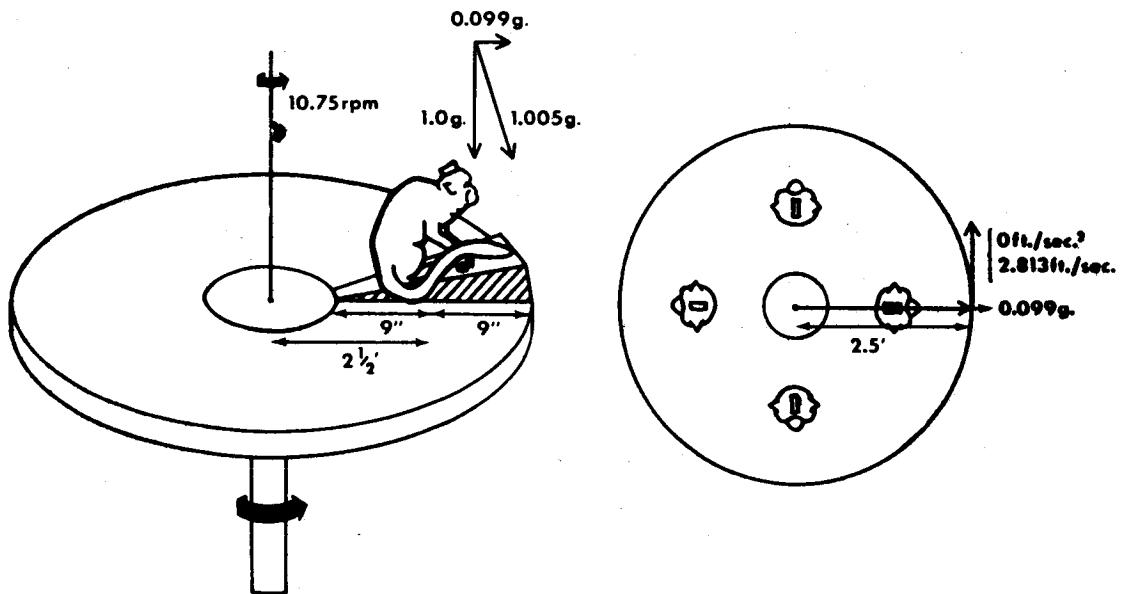
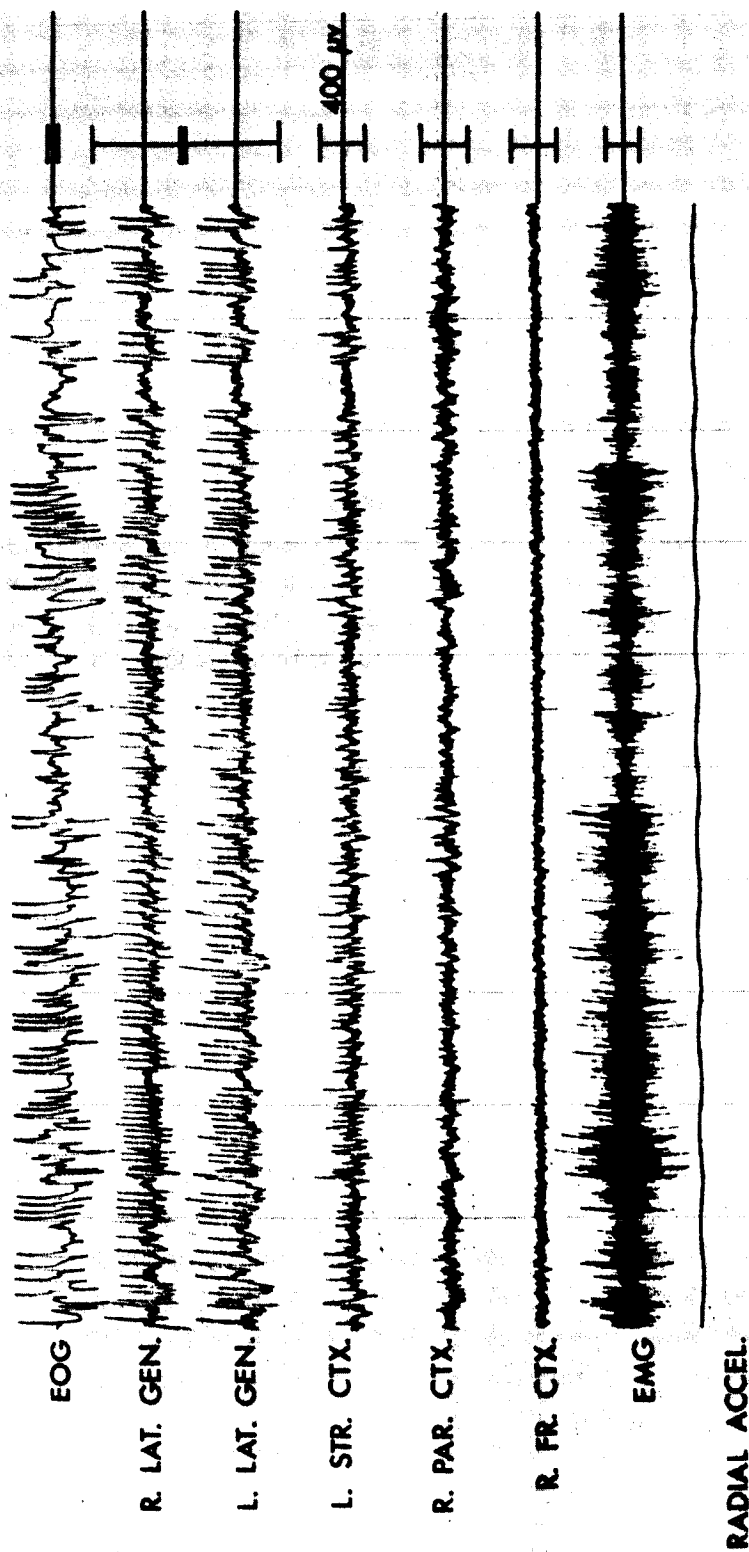


Figure 1.— Schematic diagram of the apparatus for rotating monkeys at a constant angular velocity.



# CONSTANT ROTATION



# WAKEFULNESS

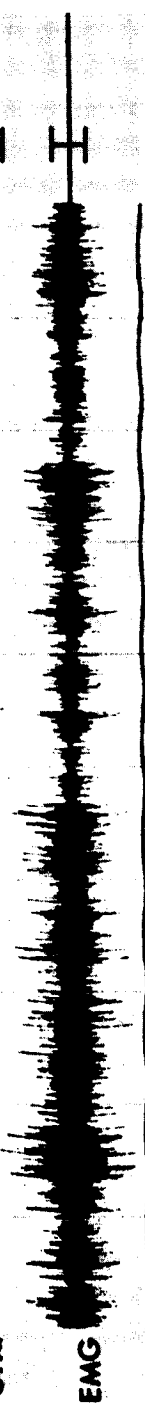


Figure 2.— Polygraph recordings from an awake owl monkey. All channels of the EEG are differential recordings from bipolar electrodes. Nystagmus, produced by head movements, is evident in the EOG.

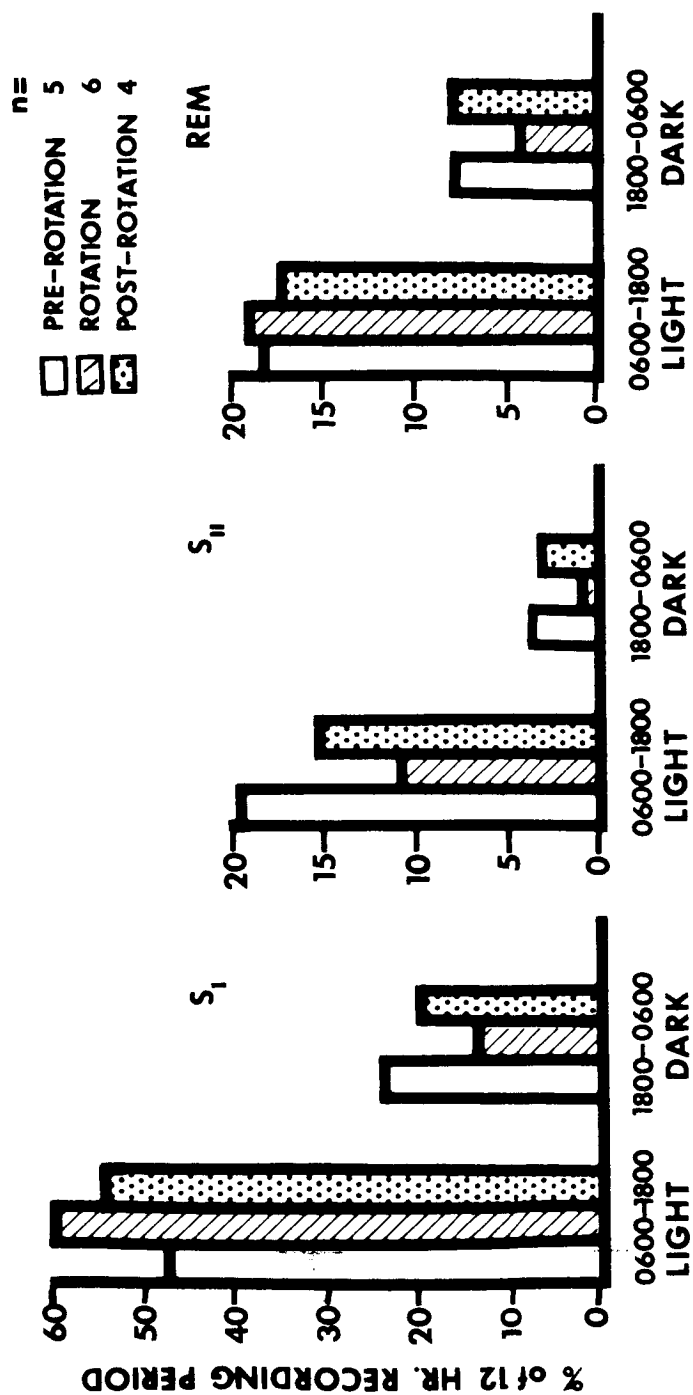
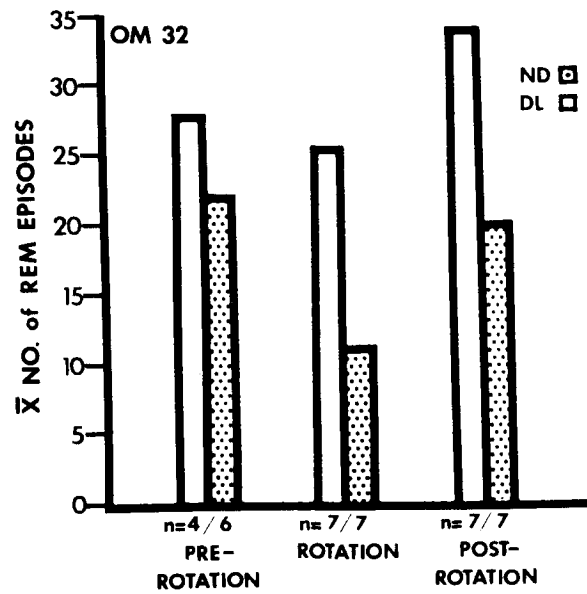
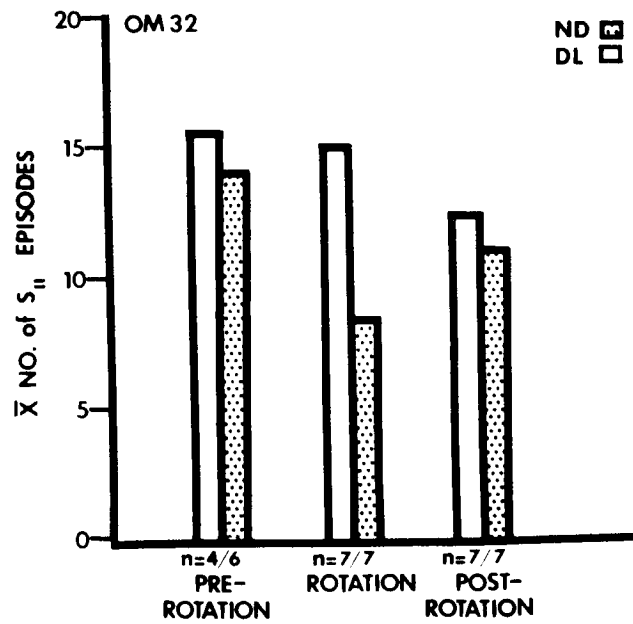


Figure 3.— Average percentage of each half of the light/dark cycle for three stages of sleep (see text for definitions). Differences for S<sub>II</sub> and REM are statistically significant for dark phases.



(a) Average number of REM episodes was significantly fewer during dark phases (ND) of rotation.



(b) Similar reduction was observed with average number of  $S_{II}$  episodes.

Figure 4.— Effects of rotation on number of sleep episodes.

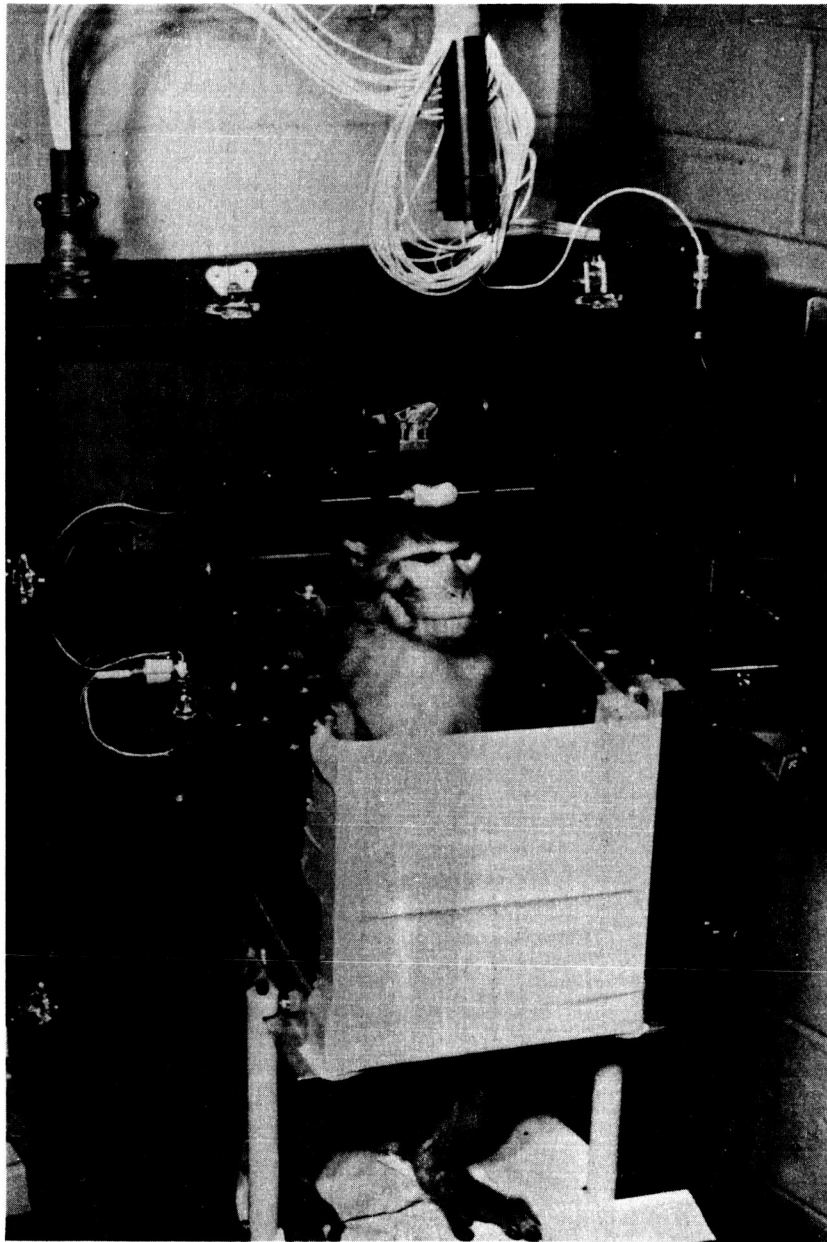


Figure 5.— View of a rhesus monkey held in combination chair and head restraints, mounted on a platform on top of a d.c. torque motor. Video camera, to the animal's left, is focused on a mirror reflecting a view of the face. Signal conditioners are mounted behind the animal in the back half of the shroud, the front half containing the chamber light and fan has been removed.

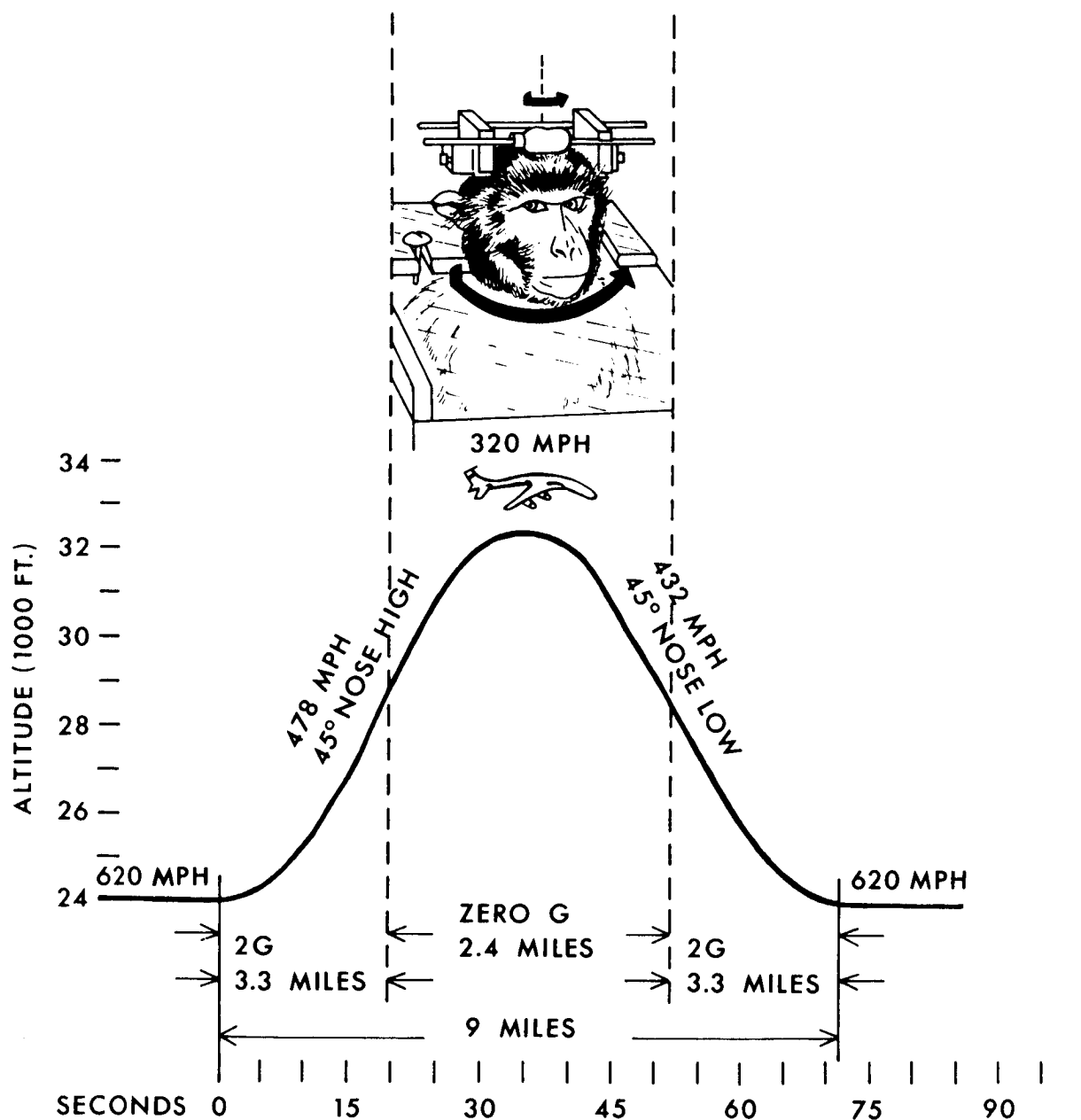


Figure 6.— Schematic diagram of the parabolic trajectory flown by a KC-135A aircraft to achieve a brief period of weightlessness. During the weightless portion of the flight, the restrained monkey is rotated around his vertical axis at a constant angular acceleration to stimulate the vestibulo-ocular reflex.

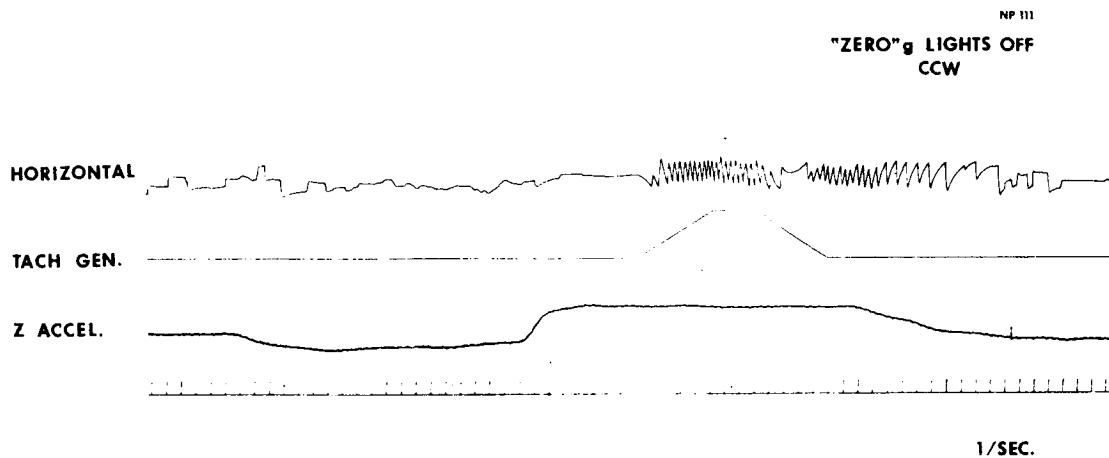


Figure 7.— Nystagmus reflex in a rhesus monkey during a brief period of zero G during parabolic flight. Upper trace is a d.c. recording of summated horizontal eye movements. Middle trace is the output of the tachometer generator of the d.c. torque motor indicating chair rotational velocity. Lower trace is the output of a Z-axis accelerometer mounted on the head restraint directly above the center of the animal's head. Rotation was counterclockwise at  $63^\circ/\text{sec}^2$ .

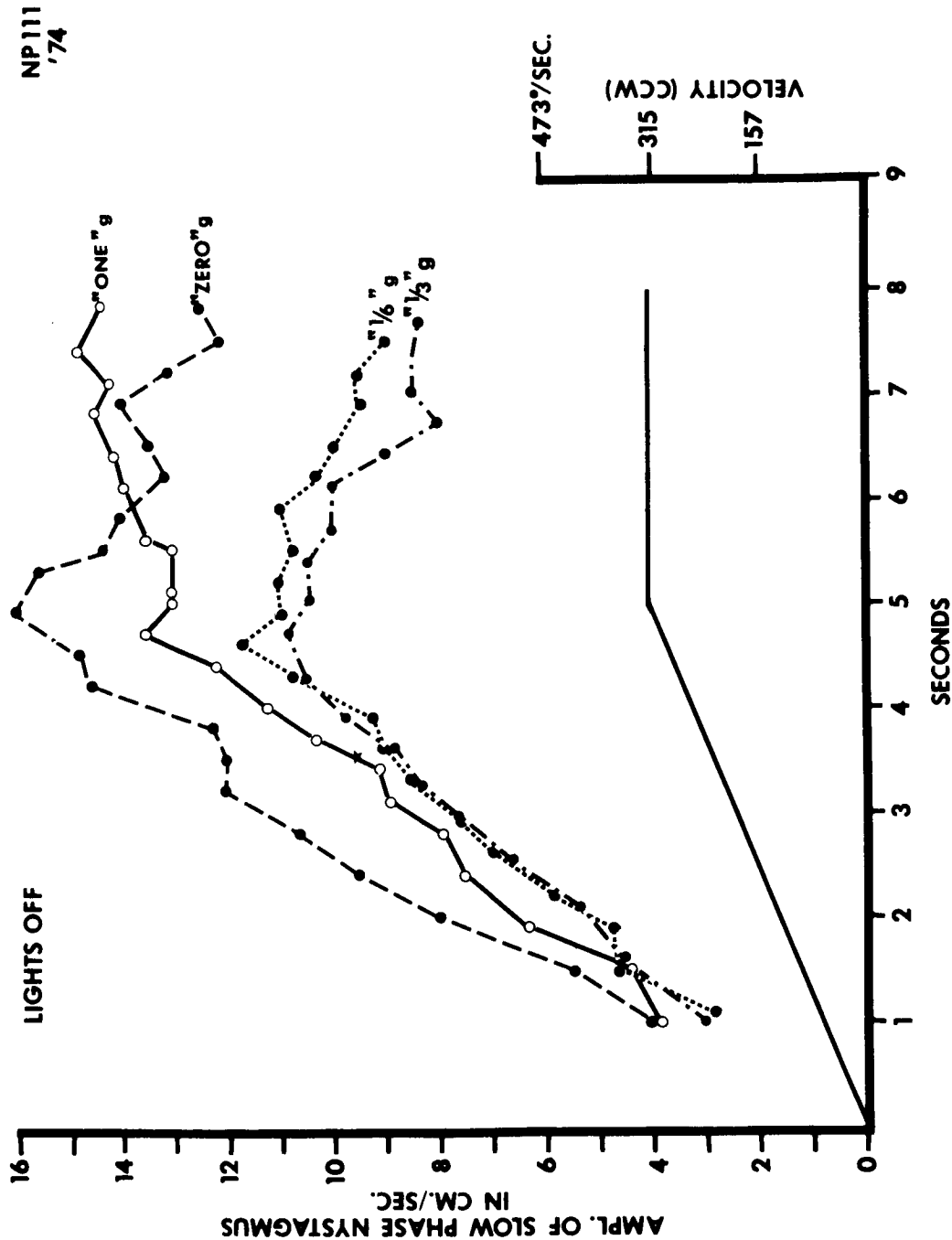


Figure 8.— Effects of altered gravity on nystagmus. Solid line represents chair velocity for 8 sec of test profile (deceleration has been omitted). Eye velocities for slow-phase component of nystagmus were estimated by measurement of EOG signal amplitudes recorded on a light-sensitive paper by a direct writing instrument. Each point represents an estimate of a separate eye movement. The stimulus was a counterclockwise angular acceleration at  $63^{\circ}/\text{sec}^2$ ; the test chamber was illuminated.

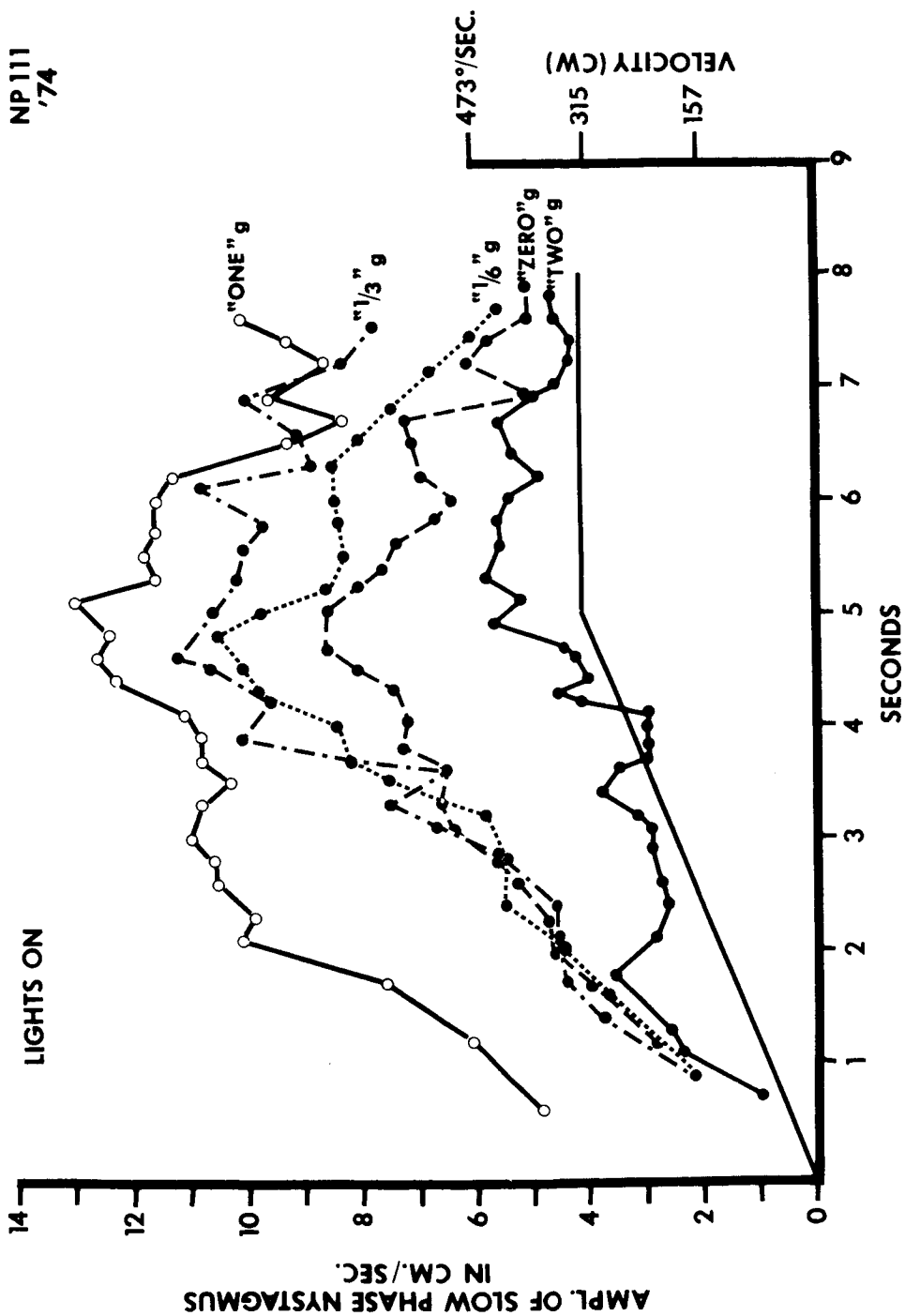


Figure 9.— Effects of altered gravity on nystagmus. Same as figure 8 except solid line connecting filled circles represents slow-phase velocities of nystagmus during a 360° turn producing a constant 2-G acceleration. The stimulus was a clockwise angular acceleration at 63°/sec<sup>2</sup>; the test chamber light was on.



# VETERINARY MEDICAL CONSIDERATIONS FOR THE USE OF NONHUMAN PRIMATES IN SPACE RESEARCH

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## INTRODUCTION

The validity of biomedical research using animal subjects is highly dependent on the use of "normal" and healthy animals. Further, the current costs of research programs dictate that minimum numbers of animals and test replicates be used to obtain the desired data. The use of healthy and standardized animals will, therefore, increase the probability of obtaining valid data while also permitting greater economy by reducing the between-individual variation, thus allowing the use of fewer animals.

Space research in particular is relatively expensive when compared to similar ground-based experimentation. The goal of the Shuttle Space Transportation System is to put payloads into Earth orbit for less cost per kilogram than has heretofore been possible. Nevertheless, the relatively large payload weight of an animal experiment, i.e., the combined weight of the animals, their maintenance hardware, food and water, and ancillary experiment equipment, will result in considerable costs simply for the transportation into space and return.

For these reasons it is mandatory that in-flight space biomedical experiments utilize only very healthy and standardized animals. To this end, a well-defined and rigidly enforced veterinary care program must be included as part of the overall management of such studies.

It is not the purpose of this paper to spell out in detail the day-to-day operating procedures and care requirements for nonhuman primates (NHP) which are selected for use in in-flight space experiments. Rather, it is my intent to discuss in broad terms those areas of concern which must be addressed when formulating such detailed plans.

## SELECTION OF NONHUMAN PRIMATE SUBJECTS

Selection of the species of NHP which is best suited for any particular experiment will depend a great deal on the constraints of the flight on which the animals will fly (e.g., the available space or weight allowance might limit the size of the animals), the scientific requirements of the experiment (e.g., the size of the hardware which is to be implanted might dictate a rather large NHP), and the availability of the required numbers of the candidate species (e.g., species on the "endangered" list would probably be very difficult to obtain or to justify for use). The responsible scientist will have

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to make the selection based on the best mix of the pros and cons developed from a thorough consideration of these constraints. Once the species has been selected, efforts should begin immediately to identify suitable individual animals for screening as flight candidates.

The large number of overt and latent disease problems associated with wild NHP's caught and held in captivity suggests that space scientists would do well to use only animals which have been born and raised in captivity under controlled physical and psychological environments. Granted, such animals will be more expensive than the wild animals, but the cost differential is rapidly disappearing, and in any case, the better quality of the test NHP will be worth it in the long run.

Candidate animals should be evaluated for physiological and psychological normalcy. There are a number of sources for information relative to standard quarantine and screening procedures for determining the health of potential NHP subjects (refs. 1-4), but a behavioral screening protocol will have to be developed for the particular species and experiment under consideration. Part of the selection procedure should include an evaluation of the animal's tolerance for the housing system to be used during the in-flight portions of the experiment, particularly if the animal is to be restrained or confined in a very small space during the flight (e.g., restrained in a couch or "pod," confined to a small transporter during launch and recovery operations, and so forth).

Only individual NHP's with high "scores" on all screening tests should be selected as potential space travelers. Once designated as a flight candidate, the NHP should be maintained under a strictly enforced veterinary care program designed to limit the animal's exposure to potentially infectious or toxic agents and to minimize environmentally induced stresses.

## ROUTINE CARE

The day-to-day procedures for the care of NHP's which are selected for space flight will depend on the species involved and need not differ significantly from the normal procedures used in any well-managed colony. However, particular emphasis should be placed on the quarantine of new animals and animals returning from satellite colonies (e.g., a temporary colony at the aerospace contractor's facility where the housing hardware is tested), limiting access to the colony to only essential personnel, the quality of the staff's occupational health program (i.e., one must minimize the chance of introducing medical problems).

Well-trained and motivated animal care technicians are essential members of the research team, and their conscientious accomplishment of the daily chores will contribute greatly towards the success of the experiment. For this reason, the animal care technicians should be kept informed of the objectives of the experiment and how their efforts contribute to the overall program. Further, project scientists and managers must not violate established procedures simply for expediency as their poor examples will be noted by the animal care personnel (e.g., if it is the established policy that persons entering an animal room must wear protective clothing and face masks, it would not be appropriate for Senator Smith to tour the facility unless he were wearing the prescribed clothing).

## GROUND-BASED STUDIES

Regardless of the species of NHP involved and the objectives of the particular experiment, "end-to-end" ground-based experiments are essential to gain experience with the entire integrated experimental system and to prove that the proposed protocol will work, including satisfactory survival of the animal subjects.

In these ground-based studies, all aspects of the experimental protocol must be included exactly as proposed for use during the actual experiment, regardless of how insignificant they may seem to be. In addition, whenever possible, the animals should be subjected to simulated launch and reentry stresses (i.e., shock, vibration, and acceleration) at the appropriate times in the "flight" and under the anticipated flight conditions (e.g., restrained in a couch in a specified orientation to the spacecraft axis and instrumented as for flight). In other words, a significant number of animals must successfully tolerate the anticipated stresses of the proposed protocol and flight regime per se, from the beginning to the end of the flight, to justify the management decision to fly the experiment.

An additional ground-based study which may provide valuable information on the response of the animals and experiment equipment to reduced gravitational forces is to expose them to short periods of weightlessness using aircraft flying parabolic trajectories. For the most part, NHP's tolerate such flights very well. An extra dividend from such tests is the experience which the research team gains by participating in a flight which requires quite similar preparations as for an actual space flight.

## INSTRUMENTATION

Recent advances in biomedical electronics have greatly increased the quantity and quality of physiological data which may be obtained from research animals. Unfortunately, this has led to a tendency to instrument animals so much as to bring into question their suitability as subjects. Also, the instrumentation may induce significant stress and thereby present a potential health hazard to the animal.

It is extremely difficult to answer the question "How much instrumentation is too much?" Obviously any instrumentation package or protocol which results in a significant mortality rate among the animals is too much. Conversely, the aseptic implantation of a sterile body temperature telemetry unit into an animal's abdominal cavity via a simple laparotomy probably would not adversely affect any biomedical experiment once the animal recovered from the surgery. Somewhere in between these two extremes is the point where the amount of instrumentation becomes unacceptable. The scientists and managers of each flight experiment will have to determine, on a case-by-case basis, whether or not proposed instrumentation for their experiment is excessive. The data from the ground-based "end-to-end" tests must weigh heavily in such decisions. If necessary, the responsible persons should have the intestinal fortitude to cancel or delay an experiment if it is questionable whether it can be successfully accomplished in space flight. It is possible to fly an experiment which has been delayed for good cause but very difficult to re-fly an experiment which has failed.

## FLIGHT OPERATIONS

The movement of the flight animals between their home colony, the launch center, the launch pad, and the recovery site may significantly and adversely affect the outcome of an experiment. It is well known that simply transporting animals from one location to another can alter their physiological responses, immunologic competency, biological rhythms, and so forth. Investigators planning space-flight biomedical studies must take into account, and design appropriate controls for, the stresses imposed on the animals simply as a result of the flight operations. Without such controls the investigator will not be able to isolate the effects of the parameter under study (e.g., weightlessness) from the nonspecific and unavoidable effects of the stresses induced by the operational requirements.

A carefully planned veterinary care program can help minimize these operational effects. Transporters which maintain the animals' environment within acceptable limits may seem to be an expensive luxury, but such hardware is necessary to protect the animal during shipment. The lack of such hardware may result in loss or degradation of the animal due to avoidable shipping problems. All flight animals should be accompanied during shipment from one point to another, and the attendants should supervise the loading, placement, and unloading of the animals into and out of any aircraft or vehicle used.

## FACILITIES

A facility designed for the housing and care of NHP's should be available at the launch and recovery sites to ensure that suitable maintenance conditions can be met. A hastily converted hangar or building will, in all likelihood, be unsatisfactory as an animal holding facility. The facility should provide a stable and rigidly controlled environment suitable for the animal species to be maintained therein. The wide range of environmental requirements for the different NHP species means that the holding facility must be very versatile and capable of providing a variety of environments, from tropical to temperate, simultaneously in different rooms. The facility should be managed by a person trained in the care of laboratory animals.

## CONCLUSION

The veterinary care program for nonhuman primates selected as subjects for space-flight experiments must be of the highest quality possible. What may seem to be a gold-plated program to persons unfamiliar with modern animal care techniques will actually be a very valuable insurance policy for the success of the experiment. The relative cost of a high-quality animal care program as compared to an adequate one may be measured in the tens of thousands of dollars, but the economic loss due to failure of an experiment would most likely run into the hundreds of thousands of dollars.

It should also be noted that what has been said about NHP's in this paper applies equally to other animal species which may be used in the space-flight studies. An extensive endocrinological

experiment using 12 rats, each costing less than \$5.00, may require the investment of \$50,000 or more. The loss of the rats in this case would also cause an unwarranted economic loss, particularly if the loss was avoidable by implementation of a good animal care program.

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# CARDIOVASCULAR STUDIES USING THE CHIMPANZEE (*Pan troglodytes*)

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## INTRODUCTION

The ultimate objective of these studies in the chimpanzee is to evaluate the effects of long-term weightlessness on cardiac dynamics. The chimpanzee was selected as the animal model of choice for these investigations because it was felt that this species would provide a more closely related surrogate for man during trial space flights of a year or longer. Despite the phylogenetic similarities between this species and man, there exists a paucity of reliable data on normal cardiovascular function and the physiological responses of the system to standard interventions. We therefore chose to examine the maximum number of cardiovascular variables which could be simultaneously monitored without significantly altering the system's performance, in order to acquire base-line data not previously obtained in this species. Further, we wished to determine cardiovascular response to specific forcing functions such as ventricular pacing, drug infusions, and lower body negative pressure.

A cardiovascular function profile protocol was developed in order to adjust independently the three major factors which modify ventricular performance, namely, left ventricular preload, afterload, and contractility. They can be altered separately by these procedures. Cardiac pacing at three levels above the ambient rate is used to adjust end diastolic volume (preload). Three concentrations of angiotensin are infused continuously to elevate afterload in a stepwise fashion. A continuous infusion of dobutamine is administered to raise the manifest contractile state of the heart.

This report summarizes our studies carried out in tranquilized chimpanzees. Some animals were studied with totally implanted multichannel biotelemetry systems, others were monitored using "hardwire" analog techniques. We wish to acknowledge the expert technical assistance of Edward Harvey (electronics) and Adam Gordon (computer programming).

## METHODS

These studies were carried out using a total of eight chimpanzees (*Pan troglodytes*).

The techniques and procedures used to instrument the chimpanzee for studies of the cardiovascular system are similar to those previously published from our laboratory (refs. 1–5).<sup>1</sup> The basic cardiovascular instrumentation "package" used for the conscious instrumented animal is illustrated in figure 1. This method of instrumentation allows for the continuous, simultaneous measurement

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<sup>1</sup> Also in "A Linearized Inductance Micrometer for Monitoring Left Ventricular Internal Diameter" by M. D. Perry, J. E. Hinds, and E. W. Hawthorne. (Submitted for publication.)

of left ventricular internal and external diameters; left ventricular, left atrial, and aortic pressures; and left ventricular and atrial electrical activity. Two approaches were used to obtain these primary data from the chimpanzee. First, a totally implanted multichannel radiotelemetry unit similar to that designed by Sandler et al. (ref. 6) and manufactured by Konigsberg Instrument Company<sup>2</sup> was used. Figure 2 is a photograph of such a six-channel telemetry unit showing the transmitter and appended transducing devices, radiofrequency switch, battery pack, and induction loop used for charging the battery. The upper half of the photograph shows a chest X-ray taken on chimpanzee Andrew one year after implantation of the unit. The placement of the transmitter, radiofrequency switch, and battery pack can be seen in the posterior gutter of the thorax just above the diaphragm. This unit differs from that previously described (refs. 6,7) in that it contains dimension transducers and has an inductance loop for repeated charging of batteries from outside the animal. In a second group of animals, the transducing devices were implanted as shown in figure 1, and the lead wires were brought outside the rib cage subcutaneously, encapsulated in a latex bag, and buried in a subcutaneous pouch at the midscapular region of the back. When recordings are desired, these lead wires are isolated and connected directly to an analog recording system.

The details of preoperative and postoperative medical care of the chimpanzee will be presented elsewhere in this symposium by Dr. Keeling. Briefly, healthy animals certified by the veterinarian at the Yerkes Regional Primate Research Center were tranquilized using ketamine (20 mg/kg) intramuscularly. An aseptic field was prepared which was bounded medially by the midline and posteriorly by the vertebral column, superiorly by the left clavicle, axilla, and the upper border of the trapezius muscle, and inferiorly by the umbilical line and iliac crest. These animals were premedicated with atropine sulfate (0.04 mg/kg) and lidocaine (10 mg/kg) 30 min prior to surgery. In three animals, direct measurement of pulsatile arterial blood pressure was made during surgery by means of right radial artery cannulation. Arterial pressure and electrocardiograms were continuously monitored and displayed on an oscilloscope throughout the operation.

### Measurement of Left Ventricular Diameters

Left ventricular internal and external diameters were obtained using the technique of inductance micrometry (ref. 2 and footnote 1). This approach is based on the principle that when a closed conductive loop of fixed cross-sectional area is placed in a magnetic field, an electromotive force (emf) is induced in the loop. The induced emf is dependent on the distance separating the loop from the magnetic field. The principal limitation of the application of this method in the past was the inherent nonlinearity between output voltage and loop separation for such a system. In the system used in these studies, two small wire-wound coils<sup>3</sup> were implanted across the transverse diameter on the endocardial surface of the anterior and posterior left ventricular wall. One coil is excited at a known frequency and voltage for the generation of a magnetic field. The second coil receives the induced emf which is linearized and input into a d.c. recording preamplifier. Each coil weighs approximately 500 mg and is 6 mm in diameter and 3 mm thickness. A system designed in our laboratory provides all the electronic functions necessary to deliver the driver power, linearize, amplify, and calibrate the output signal from the inductance micrometers.

<sup>2</sup>Konigsberg Instruments, Inc., 2000 E. Foothill Blvd., Pasadena, California 91107.

<sup>3</sup>Hazen Everett Co., 282 Island Road, Mahwah, New Jersey 97430.

## Measurement of Pressures

Implantable pressure transducers and small polyvinyl tubes were used to measure pressure. The implantable transducers are manufactured by Konigsberg Instruments, Inc. The cells used were 6.5 mm in diameter. The left ventricular pressure cell is placed 3 cm into the left ventricular cavity along with a cannula. A similar cell was implanted in the descending aorta 1 cm distal to the subclavian artery. Pressures were measured via catheters relative to atmospheric pressure by Statham P 23 DB<sup>4</sup> strain gauges simultaneously with recordings obtained from the pressure cells at the start and end of each experiment to calibrate the cells. The pressure cells are very stable and permit periods of recording up to 12 hr without appreciable drift.

## Calculation of Left Ventricular Volumes

Changes in left ventricular volumes were derived from changes occurring in the internal diameter of the left ventricle. The assumed geometry of the left ventricle throughout the cardiac cycle was that of an ellipsoid of revolution with a fixed-axis ratio of 1.5. Previous studies from our laboratory (ref. 4) show that reliable estimates of left ventricular volume can be obtained using the equation ( $V_i = 4/3 \pi R_i^3 \times 1.5$ ). In addition, stroke volume estimated from transverse dimensional changes correlates well with stroke volume obtained by use of an electromagnetic flowmeter (ref. 8).

$$dP/dt/P_{40}$$

The first derivative of the left ventricular pressure with respect to time was recorded with a Biotronex Model BL620 active differentiator.<sup>5</sup> The derivative was calibrated using the triangular wave technique. In these studies, the rate of rise of left ventricular pressure ( $dP/dt$ ) at a developed pressure ( $P_d$ ) of 40 mm Hg during isovolumic contraction was used as an index of contractility. Studies by other investigators (refs. 9,10), as well as our own (ref. 4), show that  $dP/dt/P_{40}$  is not sensitive to changes in afterload or preload.

$$\text{Mean Vcf (circ/sec)}$$

A second index of change in left ventricular myocardial contractility that we used was the change in the normalized mean velocity of left ventricular circumferential fiber shortening [mean Vcf (circ/sec)] during ejection (refs. 9,10) at any given mean developed in the left ventricular internal wall force during ejection (MDWF). Mean Vcf (circ/sec) was calculated as follows:

$$\text{Mean Vcf (circ/sec)} = (2D_{ED}) / [(D_{ED} + D_{ES})\Delta T]$$

where  $D_{ED}$  is the end diastolic left ventricular internal diameter,  $D_{ES}$  is the end systolic left ventricular internal diameter, and  $\Delta T$  is the ejection time in seconds.

<sup>4</sup>Statham Industries, R.F.D. 3, Box 74 B, Annapolis, Maryland 21403.

<sup>5</sup>Biotronex Laboratories, Silver Spring, Maryland 20902.



## End Systolic Pressure-Diameter Relationship

A third approach used to assess changes in myocardial contractility involved the examination of the end systolic pressure and end systolic diameter relationship. It has been shown in studies on isolated cardiac muscle, as well as in isolated heart preparations (refs. 11–16), that for any given afterload and contractile state, the end systolic volume is constant during variations in preload (ref. 17). Secondly, there is increasing evidence that this end systolic pressure-diameter point falls uniquely on the active-length tension curve at any level of contractility. Hence, when at any given afterload there is a shift in left ventricular end systolic pressure-diameter point, this shift denotes a change in myocardial contractility. We have developed a protocol for generation of active-length tension diagrams from the left ventricles of conscious instrumented dogs by stepwise elevation of afterload alone and identification of the end systolic pressure-diameter point at each level. Constant infusions of angiotensin II at increasing dose levels are used (0.02, 0.04, 0.06, 0.1  $\mu\text{g/kg/min}$ ) to increase afterload. We have found that these dose levels increase afterload without changes in contractility ( $dP/dt/P_{40}$ ) or heart rate (ref. 4). The sensitivity of this method for characterizing cardiac performance was tested through the constant infusion of dobutamine, which is known to selectively increase contractility without changes in mean arterial pressure, heart rate, or end diastolic volume (refs. 18–21).

## Pacing Ventricular Function Curves

Hunter and Hawthorne (ref. 22) have shown that the classical ventricular function curve, i.e., the stroke work-end diastolic volume relationship for the left ventricle can be generated through stepwise increases in the frequency of excitation of the left ventricle in conscious dogs. Further, when myocardial contractility is increased by catecholamine infusion, then the stroke work-end diastolic volume relationship is shifted upward and to the left. Thus, this approach provides another means of assessing myocardial performance.

## Lower Body Negative Pressure

Three years ago we constructed a lower body negative pressure (LBNP) chamber, a thick-walled plexiglass box, capable of withstanding negative pressures of at least  $-180$  mm Hg. The chamber is fitted at one end with an iris-type gum rubber seal. An exhaust is provided at the side which is connected in parallel to a commercial shop vacuum cleaner. A port is provided for measurement of the level of negative pressure developed when the box is exhausted. The lower half of the instrumented chimpanzee was placed in the box which was sealed at the midabdominal level when exposure to lower body negative pressure was desired (fig. 3).

## Drug Infusions

Infusions of dobutamine and angiotensin II were always made at a constant rate of 1 ml/min using a calibrated Harvard infusion pump. The infusions were always continued well beyond the onset of steady-state conditions. Data samples for computer analysis were usually taken 3–5 min after the onset of infusion and always during the steady-state response period.

$\beta$ -Adrenergic receptor blockade was produced by injection of propranolol 0.5 mg/kg body weight. The completeness of  $\beta$ -receptor blockade was ascertained by observation of the cardiovascular effects of a standard intravenous dose of isoproterenol (15  $\mu$ g) before and after propranolol administration.

### Data Acquisition and Reduction

The signals from each of the transducers described above were fed into appropriate preamplifiers. These amplified and conditioned signals were then distributed by patch panel connections to (1) a stripchart recorder, (2) a multichannel oscilloscope, and (3) an analog magnetic tape recorder for storage of all data signals. All primary data were recorded at the Yerkes Regional Primate Research Center, and selected portions were retrieved from magnetic tape for study and for detailed computer processing upon return to Washington. The computer has 16K words of main memory (16-bit words) and two direct memory access channels, allowing data transmission rates up to 625 kHz by interleaving the channels. Peripheral devices include a multiplexed 16-channel, 14-bit resolution A to D converter capable of throughput rates of 18 kHz; two moving head disc drives, each with a fixed disc and a removable cartridge providing a peripheral storage capability of 2.6 million words, accessible at a transfer rate of 45 kHz; a 7-channel digital magnetic tape unit (200 bits/in., 30 in./sec); a high-speed printer (300 lines/min); and a Tektronix 4002A graphic terminal display unit. The hardware system is supervised by an HP-DOSM operating system with special input/output routines to facilitate continuous sampling and storage of large blocks of data (up to 500,000 words).

The student's *t*-test was used for pair group comparisons and a *p* value of less than 0.05 was considered to indicate a significant difference between compared groups of data (ref. 23).

## RESULTS

The data presented here are based on studies carried out in eight chimpanzees, three of which were hardwired. Data recorded from Andrew were obtained using a totally implanted multichannel biotelemetry system; figure 4 shows a computer plot of the changes in left ventricular internal and external diameters, left ventricular pressure, and *dP/dt* at 5-msec intervals for a series of three cardiac cycles during a control period. In figure 5, a computer plot of the changes in left ventricular internal diameter, left ventricular pressure, aortic pressure, and *dP/dt* recorded from chimpanzee Ryan using hardwire methods is exhibited. In both instances, the data are reminiscent of the changes seen for these variables in other species.

### Control Data

The data presented in table 1 represent base-line data of cardiovascular function for four chimpanzees studied over a period of 40 to 67 days following surgical instrumentation of the heart. The data in each line represent analysis from a minimum of 75 cardiac cycles acquired in sampling bites of 25 consecutive cycles during a 10-min control period. The mean heart rate for the group was  $103 \pm 15$  (range 79–121) beats/min, and the mean aortic pressure (MAP) was 101 mm Hg

(range 97–106). End diastolic and end systolic volumes were similar for those measured in dogs of comparable body weights. The average total peripheral resistance for the group of animals studied was not significantly different from values obtained in dogs.

### Cardiac Dynamic Effects of Infusions of Angiotensin II in Unanesthetized Chimpanzees

Constant infusions of angiotensin II were made in the chimpanzees at dose levels of 0.02 and 0.04  $\mu\text{g/kg/min}$ . As shown in table 2, infusions of angiotensin II resulted in elevations of total peripheral resistance well over control levels. There was an increase in MAP with no associated change in heart rate or  $dP/dt/P_d$  at these dose levels. There was no significant change in end diastolic volume, but there was an increase in end systolic volume with associated decreases in stroke volume and ejected fraction. Cardiac output and stroke work decreased as angiotensin II doses were increased.

### Cardiac Dynamic Effects of Constant Infusions of Dobutamine

Constant infusions of D-L-dobutamine were administered to chimpanzees at dose levels of 5.0 and 10.0  $\mu\text{g/kg/min}$ . As shown in table 2, infusions of dobutamine caused marked increases in  $dP/dt/P_{40}$  without significant changes in end diastolic volume, heart rate, or MAP. A slight elevation was seen in total peripheral resistance (TPR). Cardiac output and stroke work were slightly elevated. A computer overlay of the changes in the left ventricular internal dimension (LVID), left ventricular pressure (LVP), aortic pressure (AP), and  $dP/dt/P_d$ , in response to dobutamine infusions at 5  $\mu\text{g/kg/min}$ , on the control data is shown in figure 6. This plot clearly shows markedly increased peak  $dP/dt$ , small changes in aortic pressure and peak systolic left ventricular pressure, no change in end diastolic diameter, an increase in velocity of transverse shortening, and a fall in end systolic diameter.

### The Cardiac Dynamic Effects of Propranolol

Propranolol (0.5 mg/kg) was administered intravenously in order to produce  $\beta$ -receptor blockade in the chimpanzee. Table 2 shows the effects of this dose of propranolol on cardiac dynamics. The derivative  $dP/dt/P_{40}$  was found to decrease by 50% of the control level. There was no change in MAP and a marked increase in TPR, end systolic and end diastolic volumes. The stroke volume, cardiac output, stroke work, and ejected fraction were all decreased.

### Evaluation of Myocardial Contractility Using the End Systolic Pressure-Diameter Relationship

The diameter-pressure loops shown in figure 7 reveal that when the left ventricle in the conscious dog is subjected to pure stepwise increases in afterload through graded infusions of angiotensin II, there exists a linear relationship between end systolic pressure and diameter over the range of afterloads produced for a given contractile state. In addition, when dobutamine is used to uniquely increase myocardial contractility during angiotensin II infusions, this relationship is

shifted to the left. The control curve and the curve depicting increased contractility tend to converge as they approach the zero pressure point of the ventricle.

In figure 8, a similar relationship was demonstrated between end systolic pressure and diameter in a chimpanzee showing that this relationship also holds in the left ventricle of the instrumented primate.

### Pacing Left Ventricular Function Curves

Figure 9 shows the stroke work-end diastolic volume relationship produced in the chimpanzee by increases in the frequency of stimulation of the left ventricle from 2.0 to 2.6 Hz. Increasing pacing rates reduced left ventricular end diastolic volume and the resultant stroke work. Thus, in the chimpanzee, as in the conscious dog, it is possible to evaluate cardiac function by stepwise changes in the frequency of stimulation of the left ventricle.

### Effects of Lower Body Negative Pressure Before and After $\beta$ -Receptor Blockade

Chimpanzee Garyn was subjected to a lower body negative pressure of -40 mm Hg three times before and during  $\beta$ -receptor blockade with propranolol (0.5 mg/kg). The results of these studies are summarized in figures 10 and 11 and table 3. These preliminary data show that exposure to LBNP (-40 mm Hg) resulted in a fall in mean aortic pressure, TPR, end diastolic, end systolic, and stroke volumes with an increase in the ejected fraction. Heart rate, cardiac output,  $dP/dt/Pd$ , and mean velocity of contractile fiber (MVCF) were increased by this procedure while no change in stroke work occurred.

When the animal was subjected to the same level of LBNP during  $\beta$ -blockade with propranolol, the MAP fell 18% from a slightly higher control value. The end diastolic volume, end systolic volume, stroke volume, and ejected fraction decreased. There was a slight decrease in heart rate and a marked decrease in cardiac output. There was no change in  $dP/dt/Pd$  while MVCF decreased, as did stroke work. The total peripheral resistance was markedly increased in response to LBNP during  $\beta$ -receptor blockade.

## DISCUSSION

### Technology

To date, we have been able to develop, with the aid of industry and the Ames Research Center, the transducing devices and techniques for surgical implantation of these devices to accurately monitor cardiovascular dynamics in chimpanzees. These devices function reliably following implantation for periods exceeding 365 days. We have studied animals with the totally implanted

telemetry units, as well as animals which are connected in a hardwire fashion. The chimpanzees with totally implanted telemetry units are more than 2 years postoperative and are currently in good clinical health. Sandler and coworkers (ref. 6) reported that the transducing devices salvaged from similar units functioned well after recovery at postmortem years later. We have not been able to test this question because all the animals instrumented with telemetry units are still alive.

All of the animals which were hardwired eventually developed infection in the subcutaneous pouch, wound dehiscence, and septicemia, and were euthanized. Thus, it appears that the totally implanted biotelemetry system is the better approach for the long-term study of cardiovascular function in conscious chimpanzees. The principal shortcoming of the biotelemetry system resides in the limited life expectancy of the present power source.

### Cardiovascular Studies

*Control data* — The preliminary control data obtained from this limited number of animals show that the indices of cardiac function are not grossly different from those seen in other mammalian species. Mean heart rate and aortic pressure were in the range for normals found in conscious dogs (refs. 2, 4, 24). These data are unlike those obtained in chimpanzees by Sandler and coworkers, and Weissler et al. (refs. 6, 7). It was suggested by these investigators that the ambient mean arterial pressure for the chimpanzee was in the hypertensive range by human standards. Our findings do not support this conclusion nor that of significantly elevated heart rates in chimpanzees.

*Changes in afterload* — The response of the instrumented left ventricle of the chimpanzee to graded changes in afterload produced by angiotensin II infusions is similar to that previously reported (ref. 4) for the conscious dog. It appears that angiotensin infusion at this level produced a "pure" increase in afterload with a subsequent increase in end systolic volume but without associated changes in contractility or heart rate. This observation is similar to the reported behavior of isolated cardiac muscle (ref. 24) where the extent of shortening and the velocity of shortening are reduced as the afterload is increased for any given contractility level. The present studies and previous work in our laboratory demonstrate that the end systolic pressure-diameter relationship obtained by this method is determined by the contractile state of the myocardium alone.

*The effects of D-L dobutamine* — Previous studies have shown that constant infusions of dobutamine result in selective changes in myocardial contractility without changes in end diastolic volume, MAP, or heart rate. The data presented here for infusion of dobutamine in chimpanzees show that the cardiovascular response in this species is similar to those observations. Dobutamine produced significant change in  $dP/dt/P_d$ , an index of myocardial contractility, without changes in mean aortic pressure, heart rate, or end diastolic volume.

*End systolic pressure-diameter relationship* — Numerous approaches to estimation of the state of myocardial performance on man (refs. 22,25) and experimental animals have been sought. Yet, it has remained difficult to estimate moment to moment changes in cardiac performance in conscious animals. It is well known that there are three factors that modulate cardiac performance, namely, preload, afterload, and contractility. Further, it has long been known that the length to which an isolated cat papillary muscle shortens under a given load is independent of the initial resting length and the amount of shortening (ref. 26). The isolated left ventricle shortens during ejection to approximate the isovolumic pressure-volume relationship. Taylor et al. (ref. 15) have

shown that the left ventricles of anesthetized, closed-chest animals eject until the volume tension relationship at end-ejection closely approximates that attained by isovolumic contractions, thus showing that the ventricle contracts until its end systolic pressure-volume point is on the active-length tension diagram. Holt (ref. 18) demonstrated in anesthetized dogs that although Starling's law of the heart relates the amount of mechanical energy set free at any beat of the heart to the length of the muscle fibers in diastole, the degree of shortening of the muscle at the end of systole is determined by the force-length relationship of the contracted muscle. More recently, numerous reports have shown (refs. 12, 13) that in the intact ventricle, the instantaneous ratio of ventricular pressure to absolute volume,  $P(T)/V$ , was almost independent of end diastolic volume (preload) and arterial blood pressure (afterload). In addition, investigators found that this ratio varied markedly with inotropic interventions. Studies from our laboratory have shown that angiotensin II infusions into conscious instrumented dogs produce an increase in afterload without changes in heart rate or contractility (ref. 4) and that infusions of dobutamine selectively increase myocardial contractility without associated changes in heart rate, mean aortic pressure, or end diastolic volume (ref. 20). By combining the two drugs, we were able to generate an end systolic pressure-diameter relationship at two levels of contractility and thereby test the reliability of this approach as a means of assessing the myocardial contractile state.

These data suggest that it is possible to assess myocardial performance in conscious dogs and chimpanzees, utilizing the end systolic pressure-diameter relationship. When a clear increase in myocardial contractility was produced by infusion of dobutamine, there was a shift of the relationship to the left as predicted from isolated muscle studies. At any given afterload, the extent of shortening produced was increased when contractility was increased. Further, the finding that the two curves tend to converge near zero intraventricular pressure tends to support the hypothesis that the unstressed volume of the left ventricle is independent of changes in myocardial contractility (ref. 13).

*Responses to lower body negative pressure* – In order to further understand the contribution of neural control of the cardiovascular system as the gravitational environment is changed, studies were carried out to test the effects of LBNP on cardiac function. We found that exposure to LBNP induces severe venous pooling with a resultant decline in heart size, stroke volume, and mean arterial pressure. The cardiovascular response to this perturbation appears to be modulated primarily by increased neural excitation of the  $\beta$ -adrenergic receptors. Cardiac output is maintained and in fact slightly increased by an increase in heart rate. Other evidence of  $\beta$ -receptor preponderance during LBNP is provided by the marked increments exhibited in the indices of contractility ( $dP/dt/P_d$  and MVCF). Additionally, the marked reduction in MAP caused a fall in peripheral resistance in the presence of a slightly increased cardiac output.

During blockade of the  $\beta$ -receptors with propranolol, exposure to LBNP resulted in a precipitous fall in cardiac output and a much smaller decline in the MAP. These changes resulted in a marked but inefficacious increase in peripheral resistance. All monitored and derived variables declined during this intervention except TPR.

The role of the mechanoreceptors in the regulation of the cardiovascular response of the chimpanzee to LBNP is unclear. Under ordinary conditions, a portion of the total cardiovascular response to a reduction of stretch on the aortic and sinus baroreceptors involves peripheral arteriolar constriction and restoration of the mean arterial blood pressure. However, during the steady-state response to LBNP, a reduced mean arterial blood pressure was sustained in the total absence of

$\beta$ -receptor vasodilatory activity. Further studies are needed to clarify these preliminary observations in conscious instrumented chimpanzees.

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TABLE 1.— CONTROL DATA FROM HEALTHY UNANESTHETIZED INSTRUMENTED CHIMPANZEES<sup>a</sup>

Name	Body wt., kg	Post-op age, days	HR, beats/min	MAP, mm Hg	dP/dt/Pd, sec <sup>-1</sup>	EDV, cc	ESV, cc	SV, cc	EJ FR, %	SW, gm m	CO, L/min	MLVPEJ, mm Hg	TPR×10 <sup>3</sup> , dynes sec cm <sup>-5</sup>
Andrew <sup>b</sup>	53	41	79±1	---	44±2	46±2	29±2	17±1	37±1	23±3	1.4	99±2	---
Ryan	25	0 <sup>c</sup>	106±1	106±3	34±2	57±1	29±1	29±1	50±1	45±1	3.0	115±4	2.5
Garyn	20	0 <sup>c</sup>	121±2	97±1	79±2	24±2	10±1	13±2	57±1	17±1	1.6	94±2	4.3
Garyn	20	66	114±2	95±1	47±1	28±1	14±1	14±1	49±2	18±1	1.6	96±2	4.3
Grant	16	0	97±2	104±3	44±1	36±2	15±1	20±3	55±9	32±3	1.9	107±3	3.2
Grant	16	67	100±2	---	43±1	28±1	15±2	13±1	47±1	20±2	1.3	109±1	---
Mean			103	101	48	37	20	18	49	26	1.8	103	3.6
± SD			15	5	15	13	8	6	7	10	.6	8	.9
SE			.7	.3	.7	.6	.4	.3	.3	.5	.0	.4	.5

<sup>a</sup>All recordings made while animals were sedated with Ketamine administered I.M.<sup>b</sup>Data acquired using telemetry unit.<sup>c</sup>Immediately post-operative.TABLE 2.— CARDIAC DYNAMIC EFFECTS OF CONSTANT INFUSIONS<sup>a</sup> OF VARIOUS DRUGS IN UNANESTHETIZED CHIMPANZEES

Intervention	HR, beats/min Mean ± SD	MAP, mm Hg Mean ± SD	dP/dt/Pd, sec <sup>-1</sup> Mean ± SD	TPR×10 <sup>3</sup> , dynes sec cm <sup>-5</sup> Mean ± SD	EDV, cc Mean ± SD	ESV, cc Mean ± SD	SV, cc Mean ± SD	EJ FR, % Mean ± SD	CO, L/min Mean ± SD	SW, gm m Mean ± SD
Control Data										
Control	104±14	98±4	56±17	4.1	29±5	13±2	16±3	54±7	1.5±0.2	23±8
Constant infusions of angiotensin II <sup>b</sup>										
Angiotensin II 0.02 .04	103±8 109±7	111±23 120±23	53±16 61±6	6.8 7.2	30±6 31±5	17±3 19±3	13±5 12±5	43±7 38±9	1.4±0.1 1.3	23±13 16±1
Constant infusions of dobutamine <sup>b</sup>										
Dobutamine 5 10	111±10 114±11	111±26 108±26	95±23 115±31	5.0 5.6	26±5 23±3	11±2 10±2	15±5 13±2	58±10 51±8	1.7±0.5 1.5±0.1	26±15 27±8
Propranolol 0.5 mg/kg										
Propranolol	77	99±4	28±1	8	33±1	23±1	10±0.5	30±1	0.9±0.1	11±1

<sup>a</sup>Results based on three sets of experiments in two chimpanzees.<sup>b</sup>Constant infusions (μg/Kg/min).TABLE 3.— CARDIAC DYNAMIC EFFECTS OF LOWER BODY NEGATIVE PRESSURE IN UNANESTHETIZED CHIMPANZEE BEFORE AND AFTER βETA ADRENERGIC RECEPTOR BLOCKADE<sup>a</sup>

Variable	Control	LBNP, -40 mm Hg		Propranolol, 0.5 mg/Kg		LBNP, -40 mm Hg	
		X±SD	%Δ	X±SD	%Δ	X±SD	%Δ
EDV (cc)	26±1	20±1.4	-21	33±1	+27	24±1	-28
ESV (cc)	13±1	10±1	-26	21±0.5	+62	17±0.5	-20
SV (cc)	12±0.4	10±3	-18	11±1	- 8	7.6±0.5	-35
EJ FR (%)	48±3	62±4	+30	35±1	-27	30±1	-13
HR (bts/min)	106	114±10	+ 8	92±1	-13	87±2	- 5
CO (L/min)	1.3	1.4	+ 8	1.1	-15	.6	-42
MAP (mm Hg)	101±18	87±10	-14	107±1	+6	88±1	-18
TPR×10 <sup>3</sup> (dynes sec cm <sup>-5</sup> )	5.8±1	5.0±0.5	-13	7.5	+29	10.5	+40
dP/dt/Pd (sec <sup>-1</sup> )	52±17	57±13	+11	25±1	-52	20±1	-19
NVCF (sec <sup>-1</sup> )	1.1±0.1	1.9	+76	0.7±0.1	-36	0.6±1	-19
SW (gm m)	18±5	18.9	+2	13±1	-28	7±1	-48
LVEDP (mm Hg)	7.2±1	-2		7.9±5	+10	6±4	-24

<sup>a</sup>This table is the result of three experiments in a single chimpanzee.

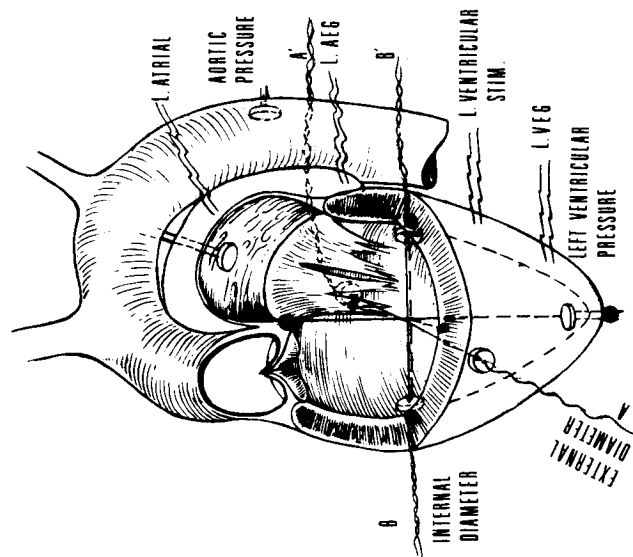


Figure 1.— Schematic diagram of the placement of transducers in the heart and aorta of the chimpanzee.

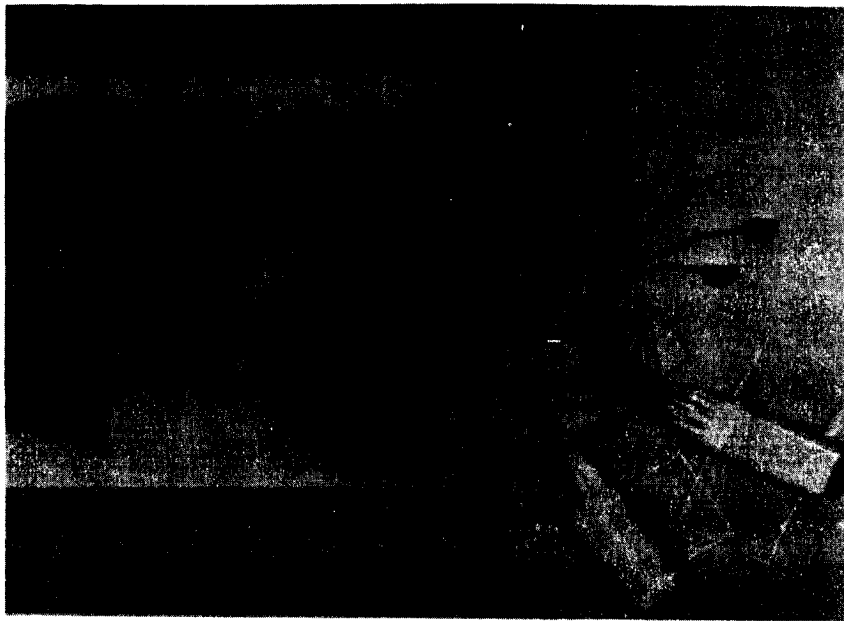


Figure 2.— A photograph of the multichannel implantable biotelemetry unit including three pressure cells, micrometers for measurement of left ventricular internal and external diameters, the transmitter, radiofrequency switch, battery pack, and inductance loop for changing batteries. The insert is an X-ray of the implanted system.

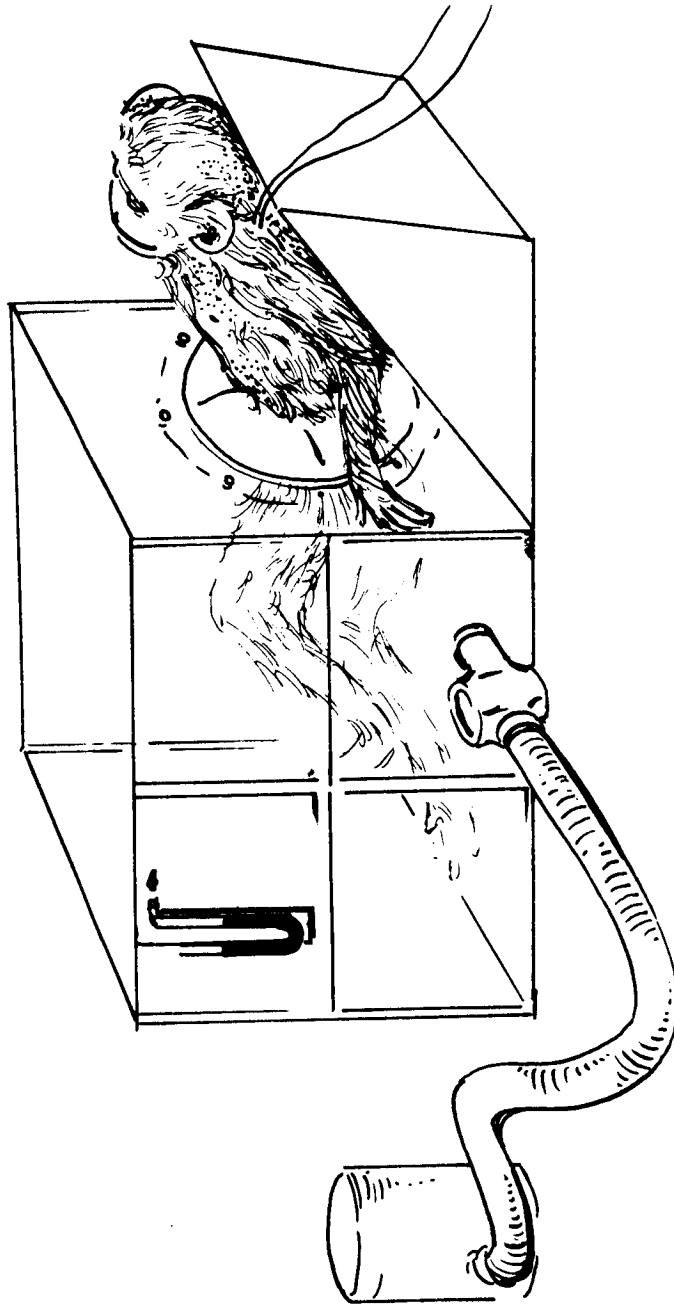


Figure 3.— A schematic diagram of the chimpanzee sealed in a lower body negative pressure chamber. The canister represents the negative pressure generator.

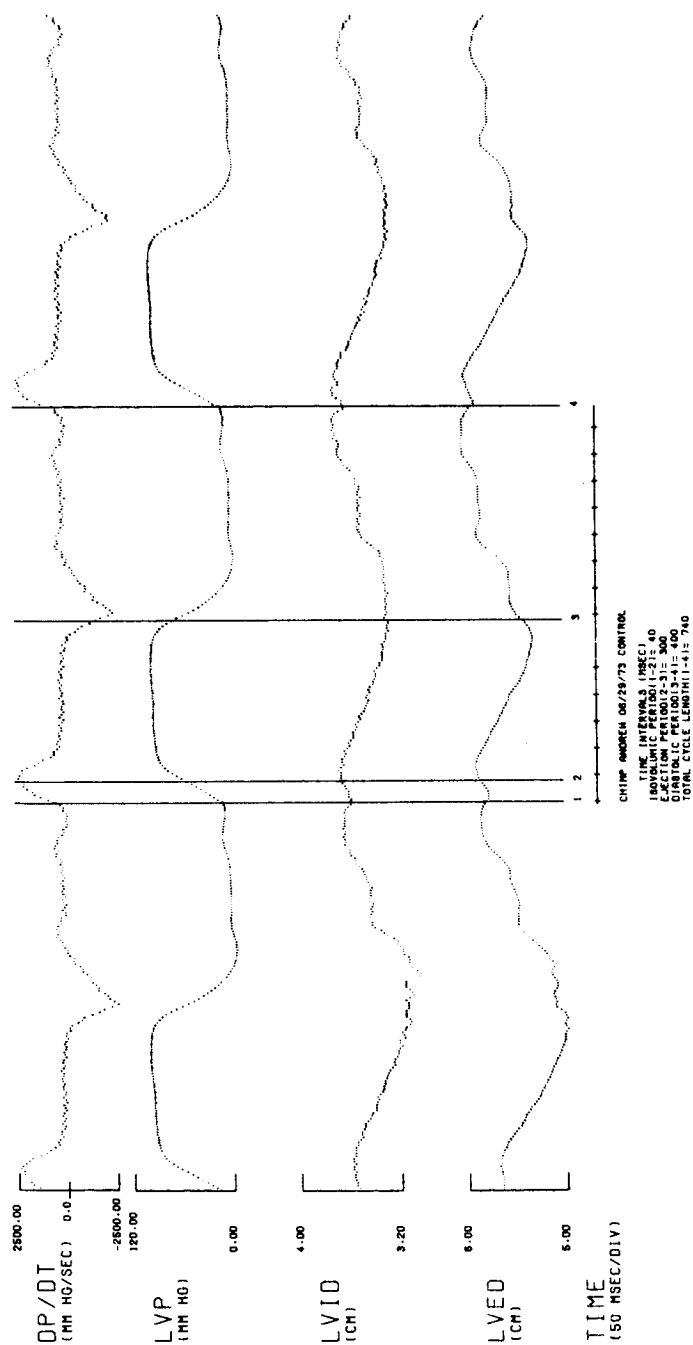


Figure 4.— A computer plot of the calibrated telemetered recording of left ventricular internal (LVIO) and external diameters (LVED), left ventricular pressure (LVP), and dP/dt in chimpanzee Andrew 41 days postoperative. The data points were taken at 5-msec intervals during a control period. The vertical lines 1–2 denote isovolumic systole, 2–3 ejection, 3–4 diastole.

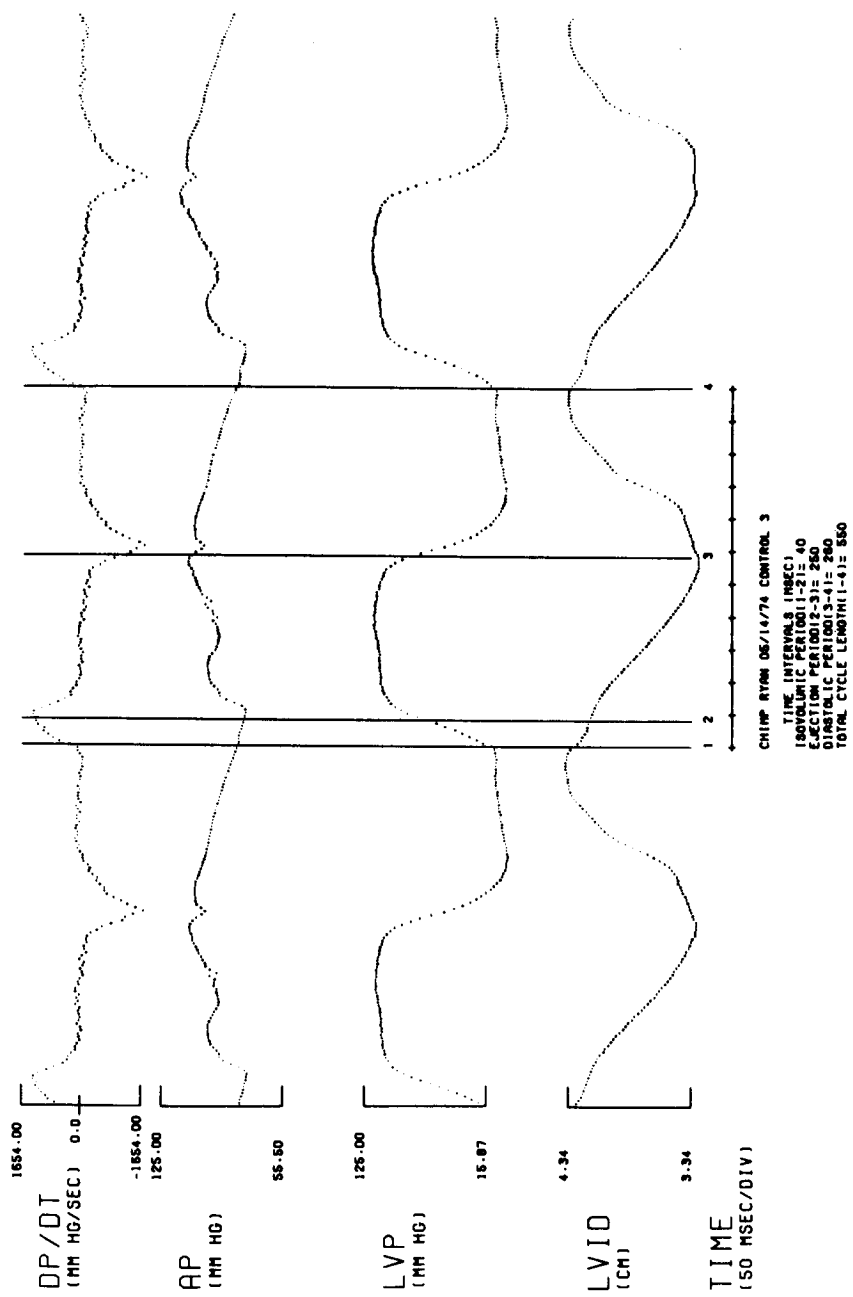


Figure 5.— A computer plot of changes in left ventricular internal diameter (LVID), left ventricular pressure (LVP), aortic pressure (AP), and  $dP/dt$  in chimpanzee Garyn. These data were obtained using the hardware technique.

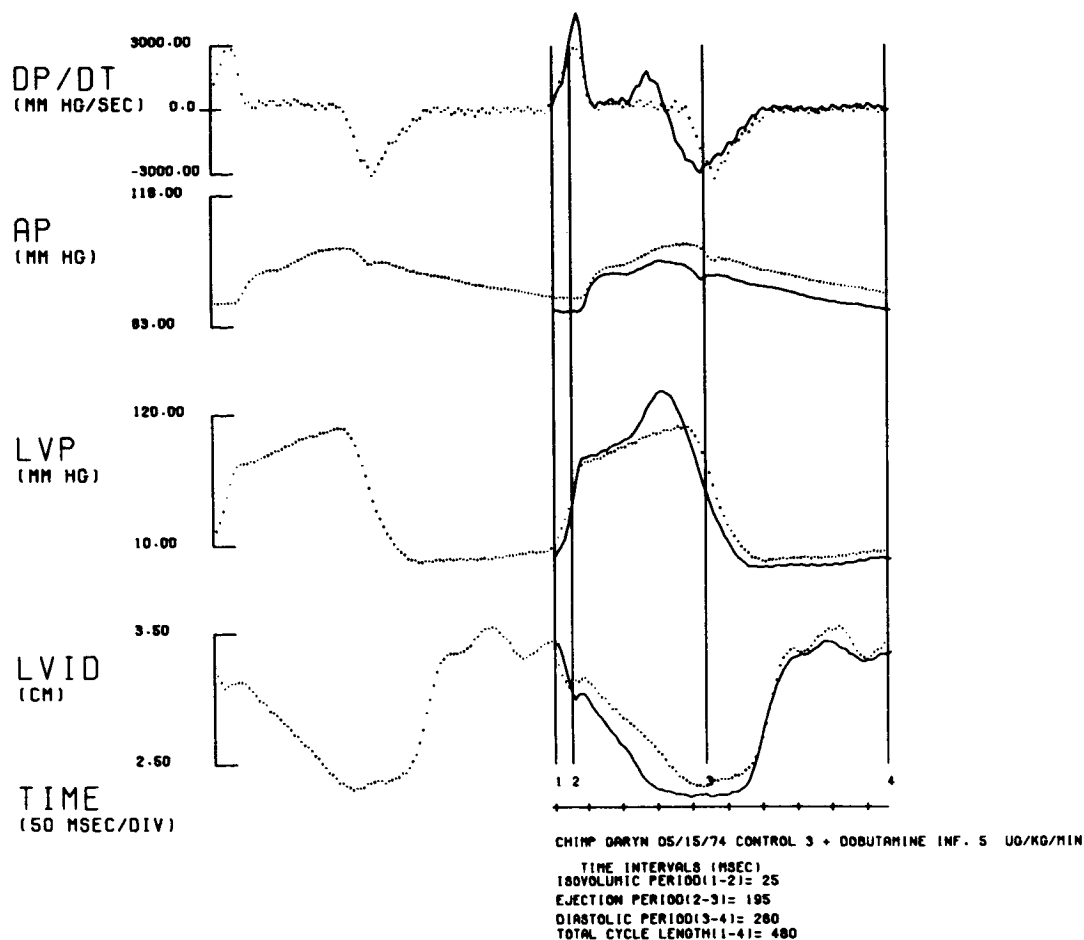
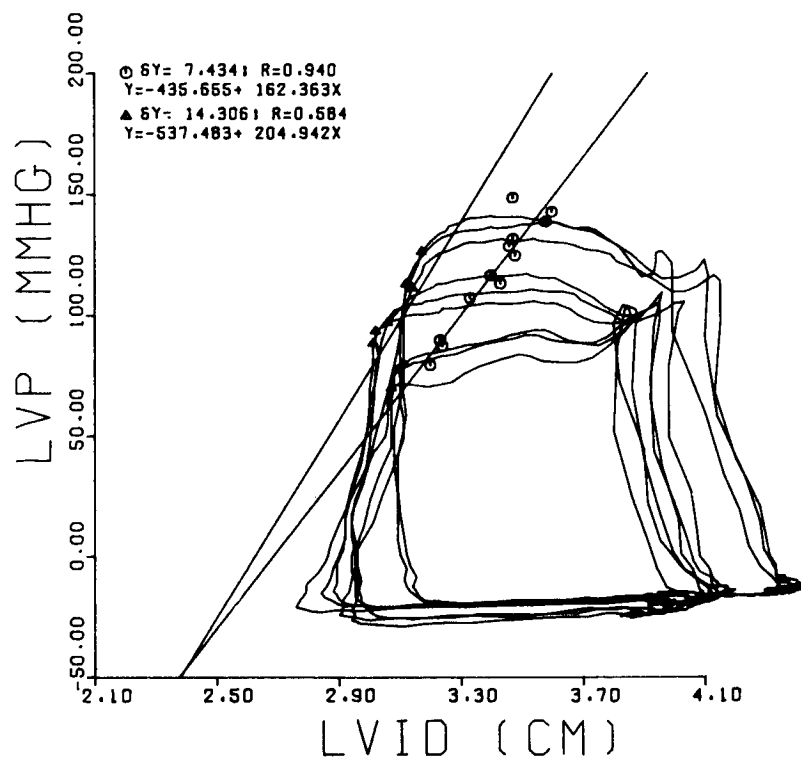
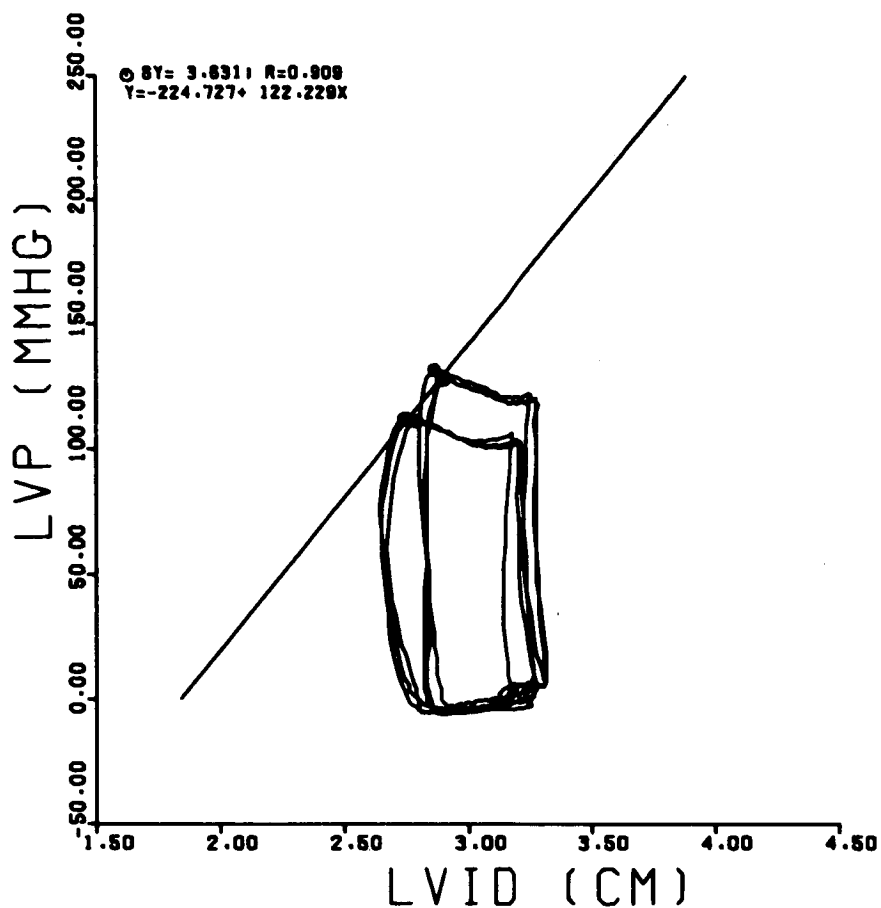


Figure 6.— A computer plot which shows the changes in left ventricular internal diameter (LVID), left ventricular pressure (LVP), aortic pressure (AP), and dP/dt from chimpanzee Garyn during a control period (dotted lines). Superimposed upon the control data is a single cardiac cycle (solid lines) taken during the steady-state response to a constant infusion of dobutamine ( $5 \mu\text{g/kg/min}$ ).



$\circ$  DOG 232 06/20/74 CONTROL & ANGIO INF. 0.02, 0.04 & 0.06 UG/KG/MIN  
 $\triangle$  DOBUTAMINE INF. 20 UG/KG/MIN + ANGIO INF. 0.04, 0.06 & 0.1 UG/KG/MIN

Figure 7.— A computer plot of the left ventricular pressure-left ventricular diameter relationship in a conscious dog before and after changes in myocardial contractility produced by infusion of dobutamine. The P-D loops shown are from cardiac cycles taken during dobutamine infusions and stepwise increases in afterload by angiotensin II infusions. The closed triangles are the end systolic pressure and diameter points for each such cycle. The line through those points is the linear regression curve for the data points obtained during infusions of dobutamine and angiotensin. The open circles and the regression curve through those points were taken from the control data produced by stepwise increases in afterload produced by serial infusions of angiotensin II.



CHIMP GARYN 07/24/74 CONTROL 4 + ANGIO INF. 0.01 UG/KG/MIN

Figure 8.— A computer plot of the left ventricular pressure-left ventricular diameter relationship throughout a series of cardiac cycles (loops) during a control period and during angiotensin II infusion in chimpanzee Garyn. The closed circles are the end systolic pressure and diameter points. The line represents the linear regression through those points.



# STROKE WORK VS EDV

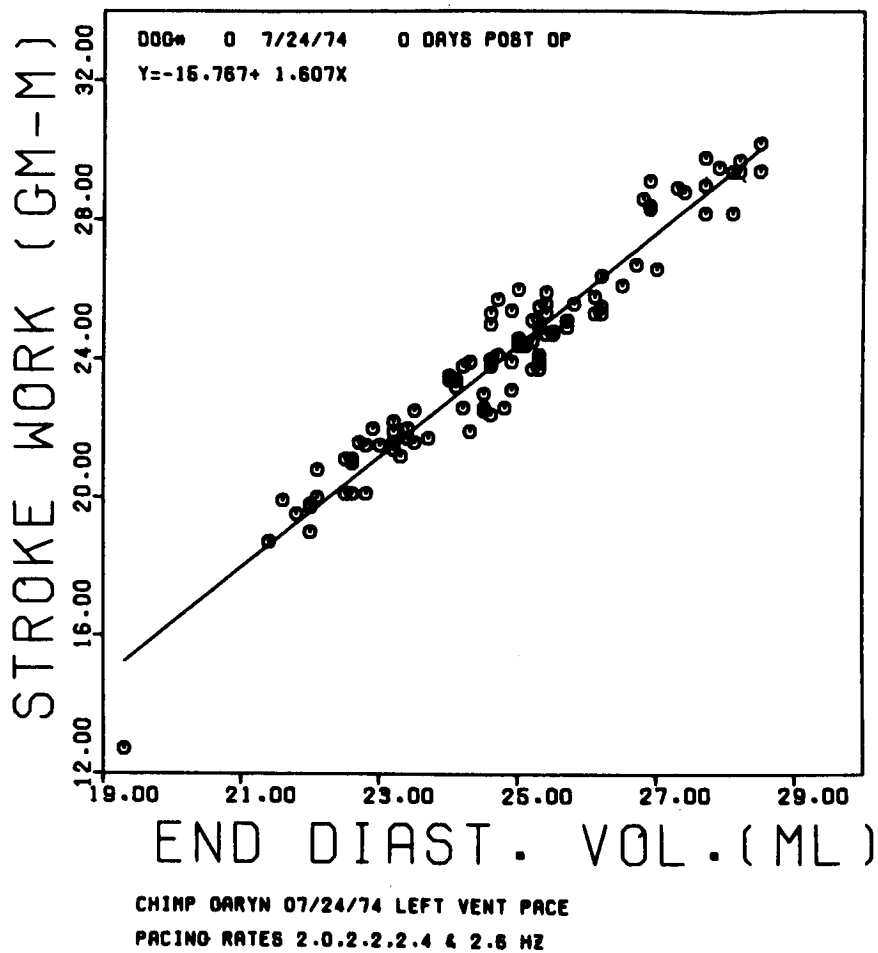


Figure 9.— A computer plot of the stroke work-end diastolic volume relationship produced by left ventricular pacing in chimpanzee Garyn during a control period.

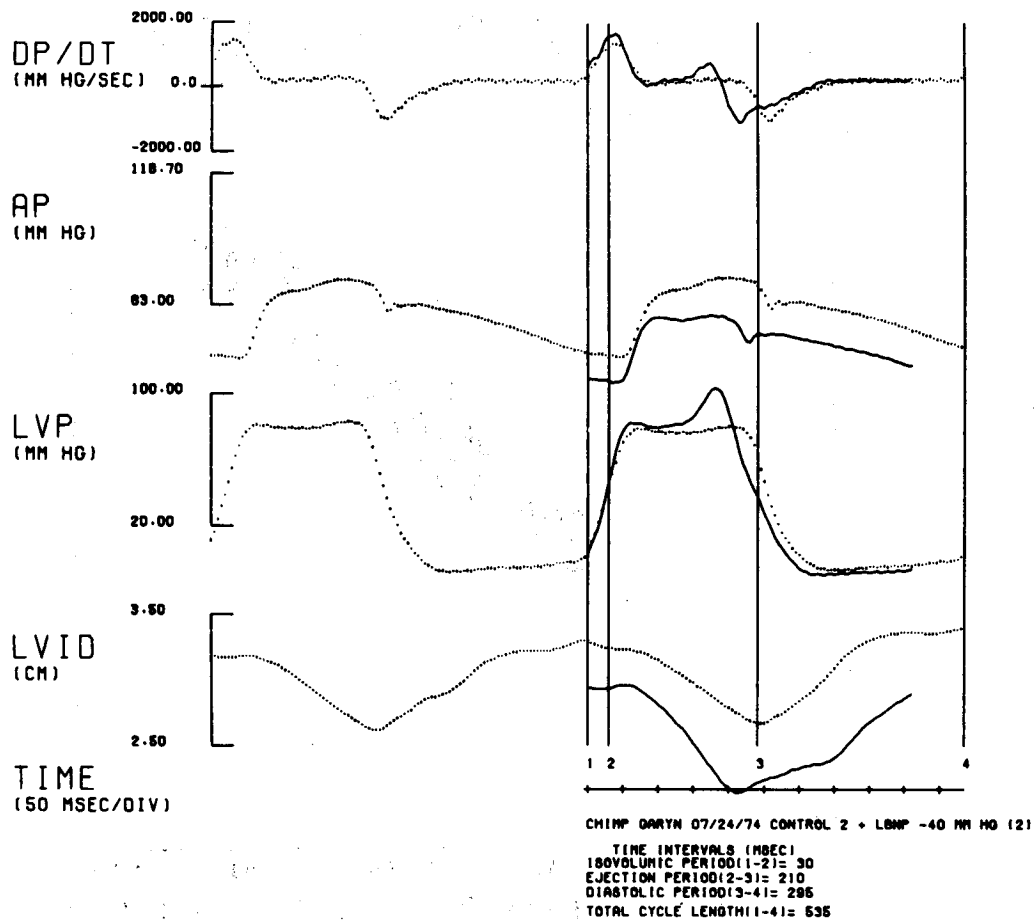


Figure 10.— A computer plot of the changes in left ventricular internal diameter (LVID), left ventricular pressure (LVP), aortic pressure (AP), and  $dp/dt$  from chimpanzee Garyn during the control period (dotted line) and during steady-state response to LBNP of  $-40$  mm Hg (solid line).

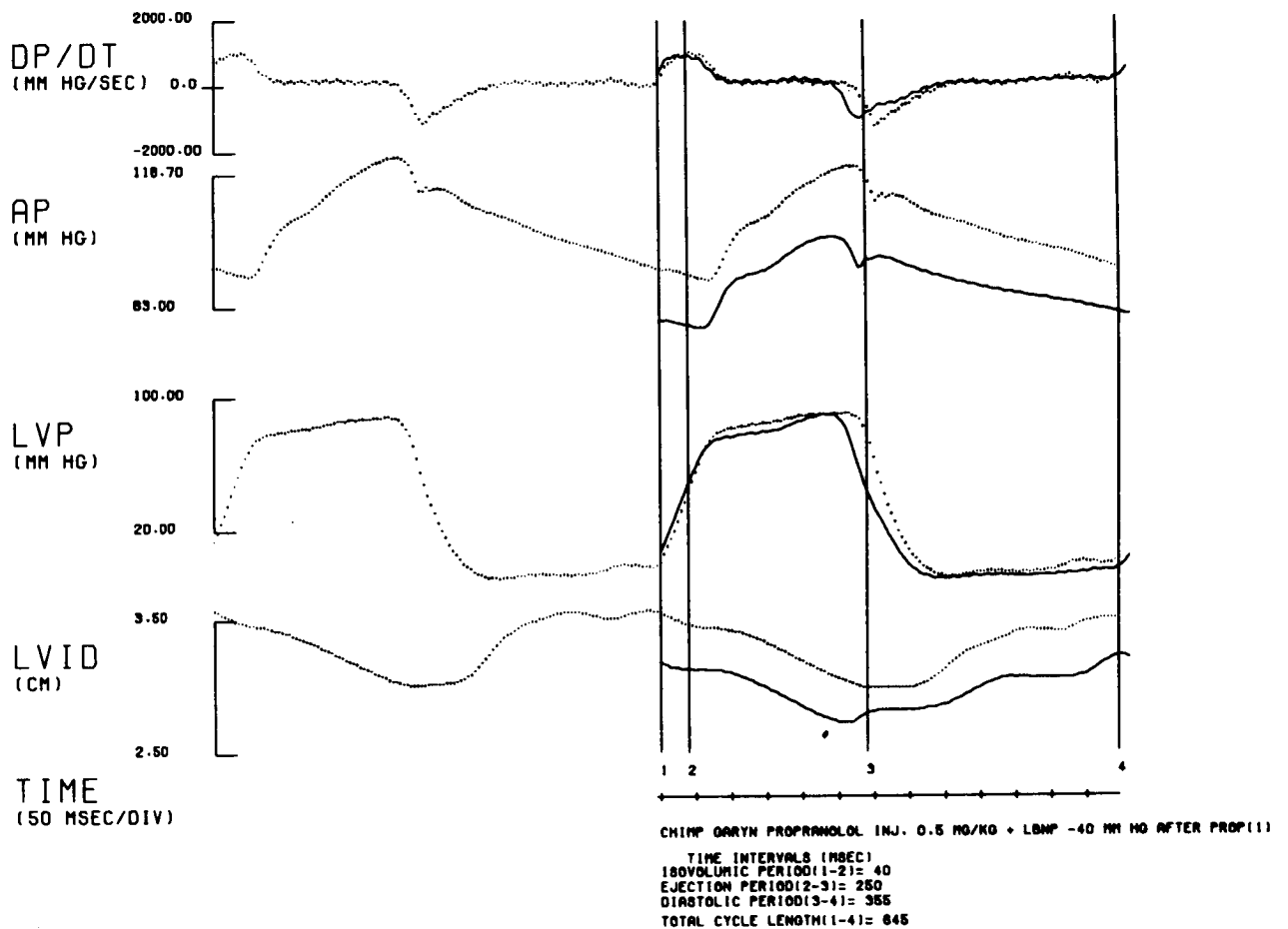


Figure 11.— A computer plot of the changes in left ventricular internal diameter (LVID), left ventricular pressure (LVP), aortic pressure (AP), and dP/dt from chimpanzee Garyn during  $\beta$ -receptor blockade with propranolol 0.5 mg/kg (dotted line) and during steady-state response to LBNP of -40 mm Hg during  $\beta$ -receptor blockade.

# INSTRUMENTATION FOR SPACE FLIGHT EXPERIMENTS

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## INTRODUCTION

### Fundamental Considerations

The selection of measurement systems for experiments conducted in the context of a space-flight must be guided by the criteria applicable to any scientific study requiring objective measurements of physiological variables. An appropriate reference frame was summarized by Stegall (ref. 1). Four steps fundamental to the process of choosing the best instrumentation system can be identified. First, the problem must be defined in terms satisfied by the measurement of specific physical properties. Second, the range of techniques available for making such measurements must be evaluated. Third, the circumstances surrounding the experimental situation must be analyzed. Finally, the three factors must be combined into a cohesive design. Careful application of these principles is necessary to achieve an optimal combination with maximum scientific validity.

An initial and critical consideration is the choice for measurement of only those primary factors necessary for the appropriate experiment, avoiding as much as possible the trap of measuring a variable because it is possible rather than essential. The interaction between choice of variable, instrumentation, and operational constraints results in many compromises. The intent is to know as fully as possible the nature and extent of these compromises, holding them to a minimum level consistent with realistic assessment of the total situation.

### Key Factors

Two factors, accuracy and utility, are of key significance for matching the operational characteristics of instrumentation to its intended use. The components of each of these factors are given in tables 1(a) and 1(b). *Accuracy* (table 1(a)) should be assessed in both static (slowly changing or steady state) and dynamic (rapidly changing or transient) terms. The *directness* component refers to the proximity of the measurement transducer to the target variable. For example, Korotkoff cuff and microphone technique for arterial blood pressure measurement is indirect because the vibrations produced in the artery must traverse multiple tissue layers before detection. An intra-arterial manometer is direct. *Specificity* refers to the degree to which a measurement is affected solely by the target variable. Some miniature intravascular pressure manometers, for example, are also extremely responsive to temperature. *Reproducibility*, or test-retest reliability, may exist even when absolute quantification is limited. *Fidelity* encompasses frequency response or sampling rate; is it sufficient for the frequency content of the sampled variable? *Stability* may be considered as the degree of baseline variation with time. Sealed manometers may change zero as atmospheric pressure

is altered, or strain gauges may drift as creep occurs in the glue bond. *Reactance* is the degree to which the biological process is altered by the measurement. Progressive deterioration of a nerve surrounded by a chronically implanted electrode may invalidate the results. *Sensitivity* includes signal-to-noise ratio, an important component of the minimal detectable change. *Range* encompasses the limits tolerated by the device and its region of linearity with respect to the load imposed by the target available.

The *Utility* classification (table 1(b)) refers primarily to compatibility between devices, subjects, and experimental setting. Wide *applicability* implies a broad range of uses; a bioelectrical signal conditioner may record the electrocardiogram (ECG), the electromyogram (EMG), the electroencephalogram (EEG), or the electrooculogram (EOG) with minor adjustments. On the other hand, the Korotkoff technique cannot be used for central aortic pressure. A technique with many different applications, such as ultrasound, is *flexible*; if it is comparatively easy to adapt to a new use, it is *versatile*. *Availability* can be extremely important; can the device be obtained commercially or must it be custom-made? Evaluation of *durability* may vary from acceleration tolerance to how long it will function when immersed in body fluids. Maintaining *compatibility* between instruments by avoiding electromagnetically coupled cross-talk or unintended activation of radiofrequency-controlled switches is often important in complicated systems. *Data format* options can vary from a meter reading providing immediate results to elaborate computer processing with long reporting delays. *Cost* is increasingly significant; is the degree of improvement in signal quality worth the extra cost? How much subject *restraint* is necessary for the measurement? The range of acceptable *invasive* techniques in space is quite limited in humans but broader in animals. Finally, *size* considerations of weight, bulk, and power requirements are becoming less important in space applications but not negligible.

The above "shopping list" sets the context for consideration of specific examples of instrumentation options to obtain physiological data from the infrahuman primate. The majority of the references will be drawn from the cardiovascular system, since cardiovascular function is particularly suitable for description in quantitative terms, and there is extensive experience with a broad range of techniques for this physiological system. Furthermore, it is a system of major significance for spaceflight because of its particular susceptibility to gravitational-inertial forces, its accessibility, and its functional activity; cardiovascular adjustments may serve as an index of the net adaptive changes produced by the space environment. In a more general sense, the approaches to obtaining significant cardiovascular information are often equally applicable to other systems. Bioelectrical signals may be as desirable for neuromuscular analysis as for cardiac analysis; development of metabolic-endocrinological understanding commonly relies on blood samples. Similar analogies exist for other fundamental variables. The purpose of this paper is to review the current status of available options as well as provide some projections for the future. This paper is intended as another step in this sequence.

Many individuals have contributed to development of the concepts and devices covered in this review. Particular appreciation is due the dedicated engineering collaborators who have not been content to rest with proof of principle, but redesigned systems many times to insure satisfactory experimental results. This close cooperation and sequential iteration are basic to successful evolution and improvement of biomedical instrumentation.

## INSTRUMENTATION IN NONHUMAN PRIMATES

The special problems of obtaining data from the nonhuman primate require either (1) sufficient restraint to prevent access to connecting lines, or (2) implantable systems totally inaccessible to freely moving animals. The restrained configuration offers the greatest number of options, ranging from noninvasive transducers such as electrodes (ECG, EMG, EEG, peripheral nerve), to invasive techniques such as chronically implanted catheters providing virtually unlimited access to blood samples or to multiple types of directly coupled transducers. Sampling intervals may be easily adjusted from continuous to intermittent with variable duration. Therefore, experience with the restrained animal will be discussed first, followed by that with the freely moving, caged animal.

### Restrained Animal

*Chronic catheterization.*— A major block of results with the chronically catheterized, chair-restrained rhesus monkey (*Macaca mulatta*) was recorded by Forsyth and coworkers (refs. 2-10). Sequential measurements of arterial pressure, cardiac output, and flow distribution with microsphere injections were made for prolonged periods during stresses such as conditional avoidance performance tests, hemorrhagic shock, anemia, anesthesia, and hypothalamic stimulation. Basic hemodynamic data for the systemic and pulmonary circulation in a similar preparation of *M. nemestrina* were reported by Rahlmann (ref. 11). The extensive studies of Mason (refs. 12-17) documented a broad range of adaptive endocrinological responses in the restrained rhesus. The above are only a few examples of the broad applicability of the restrained, chronically catheterized preparation.

The extreme environments which the chronically catheterized animal can tolerate are illustrated by vibration experiments conducted by the group at the University of Kentucky (ref. 18). Nine *M. mulatta* animals weighing from 4.8 to 8.0 kg (mean  $\pm$  SD =  $6.6 \pm 1.1$  kg) were chronically implanted with right and left atrial cannulae; various types of ventricular pressure, aortic flow, and temperature instrumentation were added to eight of the animals. Samples were withdrawn and/or catheters flushed on many different days as desired; 75 times in a single animal was typical. Survival with effective function in the eight animals ranged from 20 to 139 days (mean  $\pm$  SD =  $53 \pm 43$  days). The ninth animal originally received only left and right atrial cannulae and a thermistor temperature sensor, and was alive 18 months after the original surgery. A chronic jugular cannula was implanted after loss of the terminations from the intrathoracic lines. Catheter function in this group persisted through as many as five vibration exposures lasting 3-4 hr each, with the sessions spaced over a period as long as 6 weeks. Deaths occurred from complications caused by other transducers or during surgical attempts to remove the instrumentation because the experiment was concluded; none was due to the catheters. These animals were chaired only during the experiment. Between experiments they were freely moving in cages with the catheters and other leads stored in a special Dacron velour subcutaneous pouch. A vest was worn for added protection.

Similar long-term viability has been demonstrated by others with arterial cannulae (refs. 10, 18-21); very small sampling lines have been used in the coronary and cerebral arteries of dogs (refs. 22,23) and could be adapted for various uses in primates. Subcutaneous catheter termination in an expanded pocket allows periodic needle insertion for infusion or withdrawal without an exposed connector (ref. 24).

Results with catheterized animals in past flight tests were generally poor, but these catheters were placed acutely in peripheral vessels.

*Noninvasive options.*— Chronically implanted catheters coupled with many types of noninvasive instrumentation in the restrained animal provide an experimental preparation with wide possibilities. A chaired animal is relatively easy to instrument with electrodes, microphones, skin or rectal temperature transducers, or other similar sensors. EEG, EMG, and ECG electrodes may be of any suitable type available commercially; for instance, the standard small silver-silver chloride floating ECG electrodes work quite well in infrahuman primates. Conductive carbon buttons sewn into the skin are another approach of potential value for permanent electrodes. Flow-through systems for respiratory variables are also effective, either by covering just the animal's head (fig. 1) or enclosing the entire body.

*Pressure, flow, and dimension.*— If the experiment requires the broader range of information supplied by pressure, flow, and dimension measurements, the preparation becomes considerably more complicated. The probability of survival, especially for prolonged periods, decreases rapidly as more and more leads are brought through the skin. Survival rates can be quite variable, but with care, function can be maintained for prolonged periods. In addition to the results for monkeys noted above, representative data collected for a 1-year period are available from dogs implanted in our laboratory at Ames Research Center. Instrumentation included a left atrial catheter, ECG/pacing leads on the atria, left ventricular and aortic pressure transducers, and an electromagnetic (EM) flow transducer on the ascending aorta. In 26 dogs, mean survival was 67 days (range, 4-414 days). In eight of these animals studied continuously during the postoperative period, mean survival was  $69 \pm 44$  (SD) days (range, 12-160 days). An index to the long-term effective operation of the instrumentation is provided by the fact that the mean number of separate daily studies of the response to drug infusions was 10, with a range of 1-23 weeks. The uncontrolled causes of death were usually aortic rupture or intractable infection. The personnel and procedures were constant factors. Unexplained individual variations in tolerance seem to be the only alternative cause of the differences in survival rates. If the study design requires a very long period of function, subject availability should be assured by preparing a pool of instrumented animals.

If the expanded measurements are necessary, however, there are a number of choices. Pressure transducers of the implanted solid-state type have become progressively smaller, more reliable, and more stable. Low baseline drift rates permit calibration by periodic acute cannulation, or as often as desired through a chronically implanted catheter. Gain stability is excellent but may be checked noninvasively in a low-pressure chamber (ref. 25). Implant location may be in any body cavity desired, although acceptable accuracy is considerably more difficult to attain in low-pressure sites.

Choices of equipment for flow measurement are essentially limited to electromagnetic (EM) for continuous-wave Doppler ultrasonic (DU) flowmeters (ref. 26). The EM flow systems offer the advantages of over 30 years of experience with their use, and sources of variability and error have been carefully studied; on the ascending aorta, a satisfactory zero flow can be estimated during diastole. On other vessels, exact zero must be established by vessel occlusion. The DU flow systems are still relatively new. Zero flow reference is absolute in any vessel, and linear calibrations equivalent to EM determinations can be obtained. Nevertheless, the DU flowmeter requires very careful

adjustment to optimize signal-to-noise ratio. For nondirectional systems, potential errors due to velocity profile sensitivity are greater than with the EM flowmeter. Ultrasound is backscattered from all moving particles regardless of net direction of flow, whereas in EM systems, the induced voltage is proportional to the mean velocity of all conductors passing through the magnetic field. Furthermore, continuous-wave DU systems only estimate the mean velocity within the sample volume. This sampling window may have a dimension different from that of the major flow profile. The ascending aorta is the major site to avoid with the present generation of continuous-wave DU flowmeters; pulsed systems detecting the velocity profile are becoming available and may provide a solution to this difficulty (ref. 27). The question of the optimal technique for DU signal analysis is another of the more serious unresolved problems. On the other hand, the system's stable zero reference, low power consumption, and lightweight transducers provide strong stimuli for further improvement.

In both types, transducer-vessel relationships become quite stable with a sufficient postoperative recovery period and fibrous encapsulation (1-2 weeks), even with acceleration or vibration (fig. 2). Relative measurements over short intervals are quite accurate; the accuracy over long periods is less certain. Comparisons for calibration are best made with *in vivo* measurements using alternative techniques such as dye or thermal dilution, or radioactive microspheres. Damage to nerves and/or rupture of the aorta are everpresent hazards when cuff-type transducers are placed around the vessel.

Many options are available for detecting dimension changes. The mutual inductance principle has been used with considerable success; resistive and capacitive types have also been utilized (ref. 28). Ultrasonic techniques have proven particularly versatile. Various pulsed techniques, especially transit time (sonomicrometry), have received extensive application. An implantable echo transducer has been reported and offers great potential (ref. 29). Implanted markers such as lead beads or stainless steel screws permit tracking with roentgenography (ref. 28); equipment cost and bulk, radiation hazards, and complicated data analysis are severe limitations, especially for space conditions.

*Multiple percutaneous leads.*— Management of percutaneous leads is a constant hassle; no uniformly successful solution is available. The pouch, as mentioned earlier, is one helpful approach and protective bandages are commonly used. Special carbon buttons for fixing the exit site are promising.

### Unrestrained Animal

The disadvantages of percutaneous leads are overcome by total implantation. Implantable telemetry systems began about 15 years ago with simple, single-channel devices for transmitting biopotentials or temperature. Continued refinements in circuit design, component miniaturization, and battery power sources have provided increasingly longer life and smaller size (ref. 30-32). The pulsed radio-frequency (RF) techniques operate at micropower levels. Such basic, simple systems are relatively easy to implement and have a high selection priority when this minimum level of information is adequate.

A broader capability is available from more complex, multichannel systems. Figure 3 is an example of data obtained from a representative multichannel system. Early models for body



temperature, ECG, and/or intravascular pressures operated with readily available pacemaker cell batteries designed for human use. A typical system for ECG and three intravascular pressures consumed only 5.4 mW (2 mA at 2.7 V). Connected to two standard 1000 mA-h mercury pacemaker cells, 500 hr of continuous operation were provided. With an internal, RF-actuated switch, the system could be turned on only when data were required. Over 2 years of intermittent data transmission have been obtained in dogs and chimpanzees (ref. 25).

The electrical design and fabrication details are essential but not sufficient. Proper packaging is also critical to assure successful operation for long periods. The body provides temperature stability and impact isolation, but the high saline content of body fluids can be extremely corrosive to foreign materials. The slightest trace of moisture can cause failure of the micropower, high-impedance circuits. Therefore, all enclosures must be hermetically sealed in glass, metal, or ceramic cases. Packages treated with this procedure have been returned to function without repair, when removed 4 years after implantation, by replacement of power or transducers which failed while implanted. Biological tolerance is high. The units have been retained in dogs for more than 7 years with apparent clinical health and completely localized fibrotic changes at necropsy.

Development of a miniaturized EM flowmeter has allowed significant system expansion (ref. 33). However, multiple pressure and flow measurements require an energy source far larger than the mercury cells used previously. Although the special design of the EM flowmeter reduced its total power requirements to a few hundred mW, large peak currents (up to 0.5 A) must be available. To keep the source small while retaining long operating life, power must be periodically renewed through the intact skin. Rechargeable Ni-Cd batteries have seemed the most feasible way to meet these requirements (ref. 34). Two hermetically sealed penlight-sized cells implanted with an attached coil can be recharged inductively from a second coil placed over the skin and operated at 250 kHz. Full operation of the system with two intravascular pressures, ECG, and EM flow from the ascending aorta typically requires 180 mA, a current drain 90 times the simpler multichannel system. Two 500 mA-h Ni-Cd batteries provided about 2-1/2 hr of uninterrupted operation. Addition of an RF-actuated switch allows intermittent sampling for several weeks. Months of function are possible with recharging. In our laboratory at Ames Research Center, the recharging system has been mounted in a vest to maintain alignment between the internal and external coils and allow the animal freedom of movement while recharging is in progress, typically overnight.

The vest can also be used to increase signal transmission range. The pulse-width modulated transmitted signal is radiated from a second internal coil. A 10-MHz frequency avoids reference with the EM flowmeter or charging frequency, and a receiving coil in the vest is connected to a detector and retransmitted (transponder), shifting the frequency to 88 MHz and providing a gain in distance of hundreds of feet or more. Linearity has been better than 1 percent and the 3-dB point of output filters is 100 Hz (maximum 150 Hz). In preliminary tests, 10 dogs (20-27 kg) and 2 chimpanzees have been instrumented with the complete multichannel system. Cardiovascular data have been obtained during free roaming and treadmill exercise, over 24-hr periods, and during administration of vasoactive drugs. Effective function has varied from 2 months to more than 1 year. Battery degradation has occurred in several of the dogs after 4 to 6 weeks of implantation. Removing the battery entirely and relying solely on inductive coupling avoids the problem of battery failure and greatly decreases the size of the unit, making it suitable for smaller animals (fig. 4). As part of the implementation of this option, testing of a modified basic multichannel approach has begun. This concept utilizes a modular design with a "main frame" composed of a small, signal conditioning-transmitter unit for use with low-power transducers such as ECG, temperature, and pressure (fig. 5).

Two to four additional channels could be made available. The power supply may be a second, separate module and may or may not contain a battery, depending on the total power required by the transducer array selected and the level of short-term power storage needed. If a flowmeter is desired, it is attached as a third discrete unit. A system with two ECG leads, aortic and ventricular pressures, and temperature with coils for simultaneous inductively coupled power and signal transmission, was recently implanted in three rhesus monkeys and three small (12-16 kg) dogs; the animals and units are functioning satisfactorily (fig. 6). In other applications, mutual inductance coils for dimension measurements and accelerometers have been provided in similar units (ref. 28). Other investigators are developing implantable DU flowmeters also operating from either battery-supplied or inductively coupled power (ref. 35).

The totally implantable telemetry concept has other applications. For instance, such a system has been built with a strain-sensitive element which can be embedded in bone and becomes firmly bonded. Changes in internal bone strain may be related to alterations in bone mineralization produced by bed rest, confinement, or similar conditions producing decreased gravitational loading of the skeleton. Initial evaluation in rhesus monkeys is in progress.

### Data Acquisition and Processing

Whether the data source is the unrestrained or the restrained animal, the choices for data processing range from direct observation with pencil and paper, to completely automatic computer-controlled operation. Since all the other steps are useless without data analysis, the topic deserves much more emphasis than is possible in this overview. Surveying this area is difficult because the possibilities are so broad. Certain general guidelines may be outlined as follows: (1) "less is often more;" (2) goals limited to monitoring of physiological status are simpler to fulfill than acquisition of quantitative physiological data; (3) not only magnitude, but rate of change in state may be particularly significant; rates of change become especially important with the application of stress tests; (4) the processing and decisionmaking algorithms must be prepared in advance and are rigid; and (5) in space experiments, direct participation by the principal investigator may be limited.

"Less is often more" could even be phrased "less is *usually* more." The fewer the measurements, the fewer the sources of error and the more easily managed the procedure. On the other hand, complex biological systems with circadian and other rhythms are not easily characterized by a few isolated variables. For example, over 30 combinations of variables have been proposed as indicators of cardiac performance (ref. 36). For purposes of go-no-go monitoring, certain variables such as ECG and/or pressure may be critical. In most cases, a small number of restricted measurements will be adequate, but extreme care must be taken in selection of the minimal matrix below which a valid scientific experiment no longer exists.

Determinations of critical points are aided greatly when the restrictions imposed by computer processing are incorporated into the experimental design. Much more rigorous thinking usually accompanies building of algorithms for electronic manipulation. The complexity of computer requirements usually pays dividends by forcing repeated iterations of experimental design with overall improvement. The traditional strip-chart recorder provides real-time assessment of data quality and a form of bulk storage, but is of little aid in the interpretative decisionmaking so necessary to successful completion of a scientific protocol. A suitable computer program containing decision criteria can compress the data for bulk storage in digital format, flag unusual events for

high-rate sampling and detailed replay, supply results with trend information for verifying experimental progress, and maintain control over the test sequence.

Automatic data processing is especially significant for the space experiment. Provision for function during periods without ground contact, especially in the absence of the principal investigator, is best made by computer-aided techniques. The vast quantities of data generated in multivariable experiments are excessively tedious to analyze, another reason for seeking computer assistance.

A footnote to this section concerns the possibility of interference between the many RF-based spacecraft activities and signals acquired from implanted telemetry. Noninterfering operation in space flight environment is far more significant than in ground-based experiments. Special arrangements may be required for frequency selection, shielding, and related factors. Simulations on Earth seem to be a particularly meaningful approach to answering these and other similar considerations noted in the accuracy and utility categories (table 1).

## MEASUREMENT ENVIRONMENT

### Prototype Flight Tests

In early American experiments on obtaining data from animals during flight, several anesthetized monkeys were instrumented for respiration rate, electrocardiogram, and direct arterial and venous pressures. In 1961, electrocardiogram, respiration, and rectal temperature were recorded from a chimpanzee performing psychomotor tasks. A second chimpanzee flight test in 1961 included arterial and venous pressure measurements through fluid-filled catheters. The most heavily instrumented animal tested in the American program was a *Macaca nemestrina* flown in 1969. A total of 33 channels of telemetered physiologic data were attempted, including 14 for various bioelectric variables, 6 for cerebral and rectal temperatures, and others for variables such as arterial and venous pressures through fluid-filled catheters. Both the flight animal and two of the ground controls died before completion of the planned flight duration. No subsequent flight tests with large animals have been made by the United States.

The Soviet program utilized dogs in its large-animal experiments; between 1949 and the 1960's, 40 flights using unanesthetized dogs were made. The usual measurements obtained were (1) electrocardiogram, and (2) blood pressure from a carotid artery positioned in a skin flap. Respiration rate and electromyograms were also obtained occasionally. The longest flight of 22 days included two dogs partially restrained in a pod and fed by gastrostomy. Electrocardiograms, phonocardiograms, and carotid pulse signals provided major primary cardiovascular variables. Attempts to withdraw blood and to measure intravascular arterial pressure were unsuccessful. No significant flight tests with dogs have been conducted since 1966. Details of the previous flight experiments are contained in the paper in this conference by Sandler (ref. 37).

### Simulations

The results of flight tests indicate that relatively large animals can be placed and maintained in the space environment for prolonged periods. Improved instrumentation of the type discussed in

this paper implies a much higher probability for successful measurement of significant variables in future flights. The final configuration for this instrumentation must reflect the restraints of the environment. Previous experience and projected flight modes suggest the options summarized in figure 7.

A prototype restrained-animal experiment in a closed system has been under development by the Environmental Physiology Laboratory at the University of California in Berkeley. This system includes (1) a fiberglass pod, housing a 10-12 kg monkey provided with feeding and watering devices and an air convection system for excreta collection, and (2) instrumentation for recording food and water consumption, environmental temperature, and gas composition. The concept is compatible with sampling of physiological variables using biotelemetry and the device can be used to produce lower body negative pressure. It can be adapted for other types of animals of different species or sizes, and can sustain an animal for short or long periods. The paper by Pace and associates in this conference describes the pod system in detail (ref. 38). Such a system could be attended or unattended.

An open system could include either a restrained (chaired) or unrestrained caged animal. The easier access into a cage could simplify vascular sampling or special acute tests, but other management aspects, such as environmental control, could be more difficult.

As part of the process of clarifying the experimental options, a series of simulations has begun to evaluate future life sciences experiments for the manned flight laboratory designated as Spacelab, for payloads planned in the early 1980's. Concepts have been tested in mockups at the Ames, Marshall, and Johnson Space Centers. For example, in the extensive simulation of an attended experiment recently conducted at Johnson Space Center, two investigators functioned in a representative Spacelab environment for 1 week (fig. 8), conducting a total of 12 experiments. Two fully instrumented dogs were part of this package. Percutaneous leads from the dogs provided capability for measurement of right and left atrial, aortic, and left ventricular pressures, ECG/pacing leads on the heart, ultrasonic transit-time left ventricular dimension, and an EM flow transducer on the ascending aorta for cardiac output. Measurements were made on one dog each day. The investigators obtained control data and performed sequential left ventricular function curves using a volume load administered through the left atrial catheter. They withdrew multiple blood samples from each other and performed many other tasks as well.

These preliminary evaluations of operational procedures, man-machine integration, and data-handling techniques are representative of the effort to improve definition of tasks prior to final design and construction of hardware, making more efficient use of the investigator's effort and helping to control costs.

## FUTURE DEVELOPMENTS

In addition to the attended Spacelab mission of 7-30 days dedicated to life sciences experiments, other modes are under investigation. Self-contained "carry-on," highly automated experiments may be possible as part of missions dedicated to other disciplines. Unattended and periodically visited free-flying satellites launched from the Space Shuttle (Biomedical Experiment

Scientific Satellite, BESS) are also being considered. BESS experiments could last up to 6 months, weigh 450-1360 kg, and occupy a volume of 11-25 m<sup>3</sup>. This configuration would provide a link between the relatively brief duration of the Space Shuttle and the long-term attended facility of a manned orbiting space station or planetary mission. These options are discussed in detail in the minutes of this conference (ref. 39).

The emphases in future developments follow from the likely experimental modes. The attended, restrained animal suggests experimental possibilities based on periodic blood samples; injection of pharmacological agents, radioactively tagged compounds or microspheres; and angiographic and similar roentgenographic techniques. Procedures such as recharging of implanted batteries can be managed more readily, and protocol variations can be instituted as conditions warrant. The unrestrained animal offers advantages of minimal effects from confinement, but tethered instrumentation must be limited for either the attended or unattended configuration. For the unattended nonhuman primate, the logical direction to pursue is with completely implantable, telemetered data sources. Reasonable expectations for the near term include progressively smaller implantable units with more options. Smaller and more stable pressure transducers can be made. An implantable, pulsed DU flowmeter, including velocity profile capability, has received initial testing in an acute animal experiment (fig. 9; see also ref. 40). Inductively coupled power transmission will provide indefinite continuous operation of multielement units (ref. 34). *In situ* transducers for rapid, accurate sampling of biochemical variables have developed much more slowly than for bioelectricity, temperature, pressure, flow, and dimension. A swallowable system for pH measurement is nearing completion (ref. 41). Miniaturized infusion-withdrawal pumps can be carried in a backpack.

Over the long term, an implantable ultrasonic echo telemetry unit can be expected with an array for more accurate volume calculations. Improved batteries will allow higher power consumption and further lessen the need for restraint. Transducers for measurement of nerve traffic are urgently needed, as is a broad range of biochemical sampling systems. Measurement of glucose and oxygen levels in the tissue interstitial space will likely be among the first systems available (refs. 42,43), and new approaches combining ion-selective and gas sensing membranes with specific enzymes appear promising (ref. 44).

The above samples cannot possibly be all-inclusive, but are intended to be representative of the present and future prospects in instrumentation for use in space experiments.

## SUMMARY AND CONCLUSIONS

Continuing changes in the configuration of space laboratories increasingly permit applications of the same criteria to experiments in space as to those on Earth. Details regarding the Shuttle-transported Spacelab are beginning to emerge and indicate the study options will be much broader in the future. The Spacelab is much larger and more fully equipped than past vehicles, although it cannot be as complete as an equivalent ground facility. There will be obvious limitations on weight, size, and animal housing, which must be considered in the shared laboratory. Furthermore, the principal investigator may or may not be a passenger. If present onboard, the scientist will have responsibility for many other experiments. If not, the onboard representative is unlikely to have

extensive training or experience in the particular specialty. Therefore, particularly in the early missions, prudence indicates the desirability of keeping the initial experiments as simple as possible with minimal onboard adjustments. Nevertheless, the emphasis in choice of instrumentation lies primarily with good experimental design, rather than meeting the limitations imposed by the space environment. Current capability and future prospects in instrumentation suggest a broad range of resources for conducting an in-depth evaluation of the biological significance of gravitational stress and of the special environment of space.

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TABLE 1. – OPERATIONAL CHARACTERISTICS

(a) Accuracy

**STATIC AND DYNAMIC**

- |                   |               |
|-------------------|---------------|
| ● DIRECTNESS      | ● STABILITY   |
| ● SPECIFICITY     | ● REACTANCE   |
| ● REPRODUCIBILITY | ● SENSITIVITY |
| ● FIDELITY        | ● RANGE       |

(b) Utility

- |                 |                |
|-----------------|----------------|
| ● APPLICABILITY | ● DATA FORMAT  |
| ● FLEXIBILITY   | ● CONVENIENCE  |
| ● VERSATILITY   | ● COST         |
| ● AVAILABILITY  | ● RESTRAINT    |
| ● DURABILITY    | ● INVASIVENESS |
| ● COMPATIBILITY | ● SIZE         |

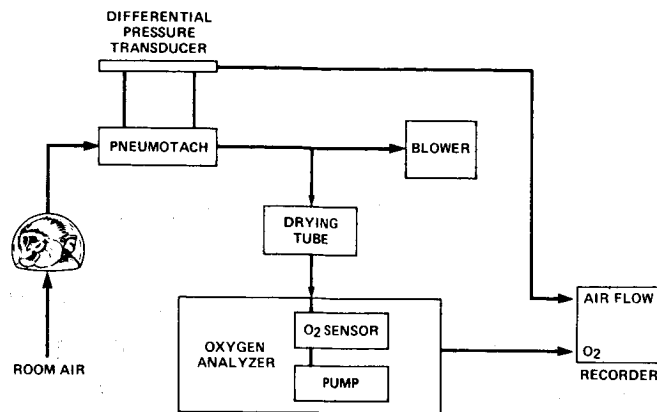


Figure 1.— Open circuit system for noninvasive measurement of oxygen consumption in conscious monkeys (developed at the Wenner-Gren Laboratory, University of Kentucky; Fleisch pneumotachometer, Instrumentation Assoc., Inc.; pressure transducer, 10303, Statham Instruments; oxygen analyzer, Electrochemistry, Inc.).

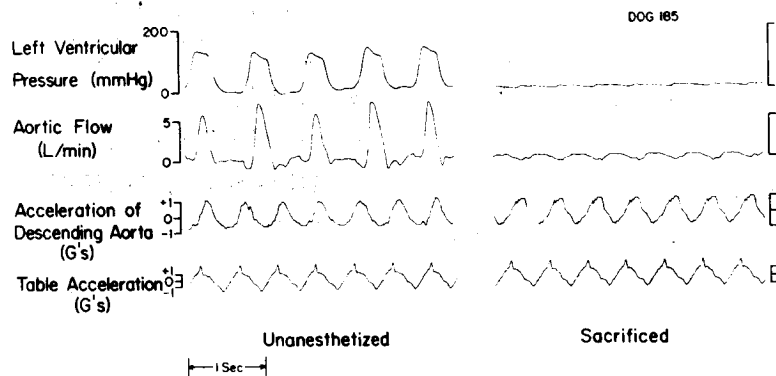


Figure 2.— Representative waveforms from multiple chronically implanted, directly-connected transducers during vibration. The postmortem stability indicates the firmness of the bond between transducer and tissue (experiment conducted at the Wenner-Gren Laboratory, University of Kentucky).

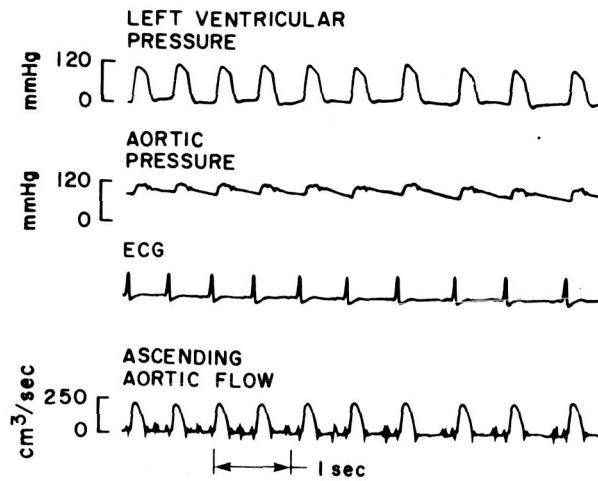


Figure 3.— Representative cardiovascular data from a totally implanted telemetry system.

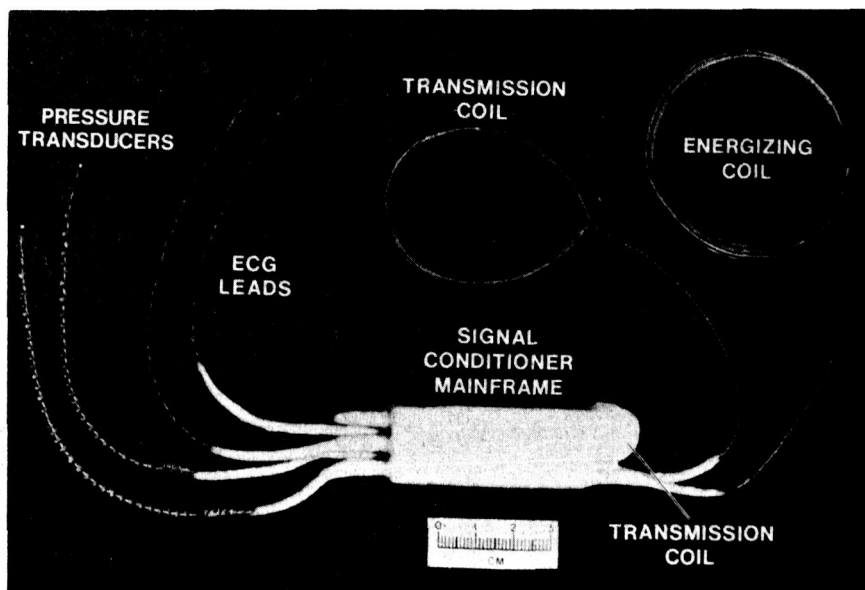


Figure 4.— Recently developed multichannel telemetry unit. The power supply is inductively coupled with no internal batteries.

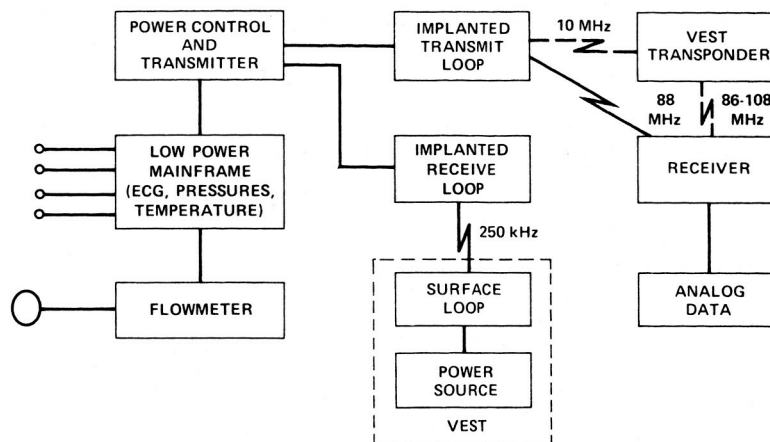


Figure 5.— Representative options provided by a modular concept for implantable telemetry systems.

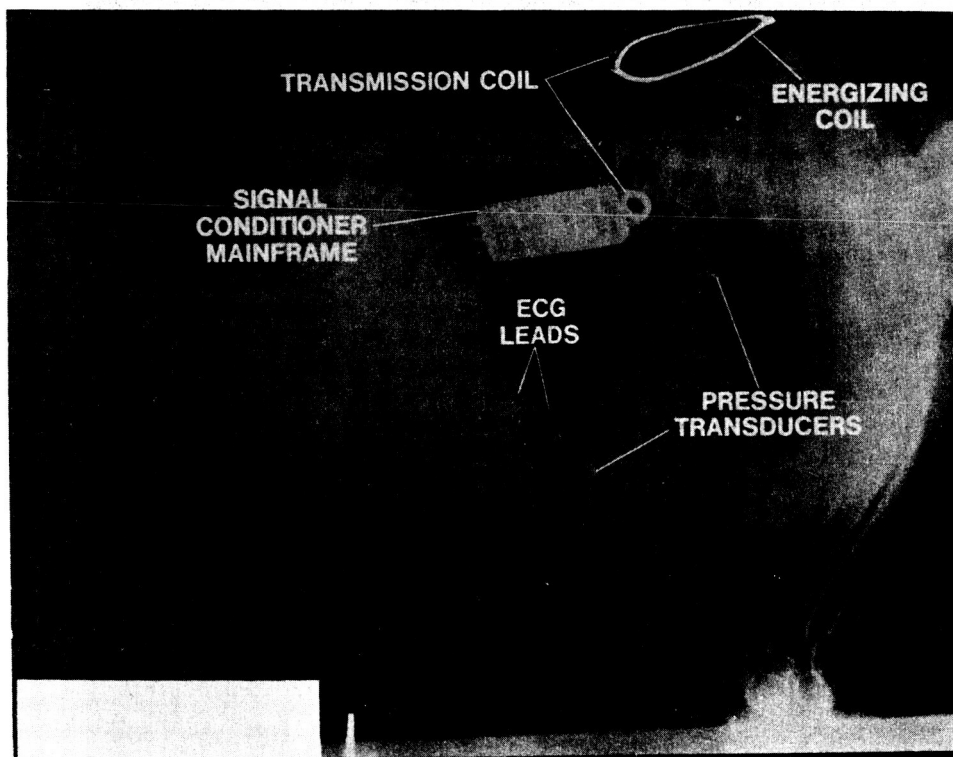


Figure 6.— Radiograph of an implanted telemetry system in a dog. Placement in the left posterior gutter is well tolerated.

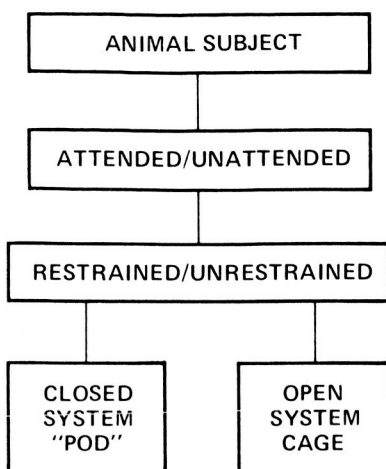


Figure 7.— Summary of major design options for spaceflight experiments.

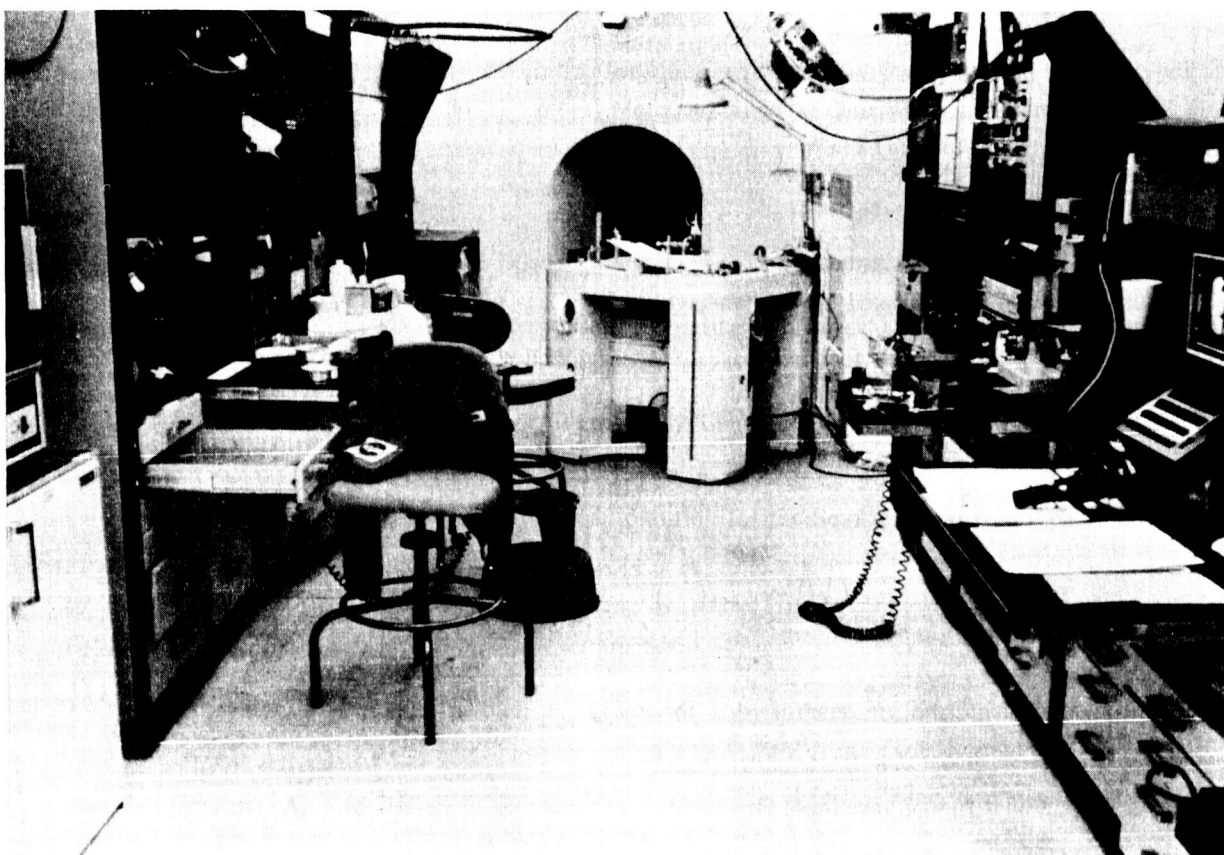


Figure 8.— A Spacelab configuration for simulation of procedures and testing of proposed experiments. (From Johnson Spaceflight Center, Houston, courtesy of Dr. Story Musgrave.)

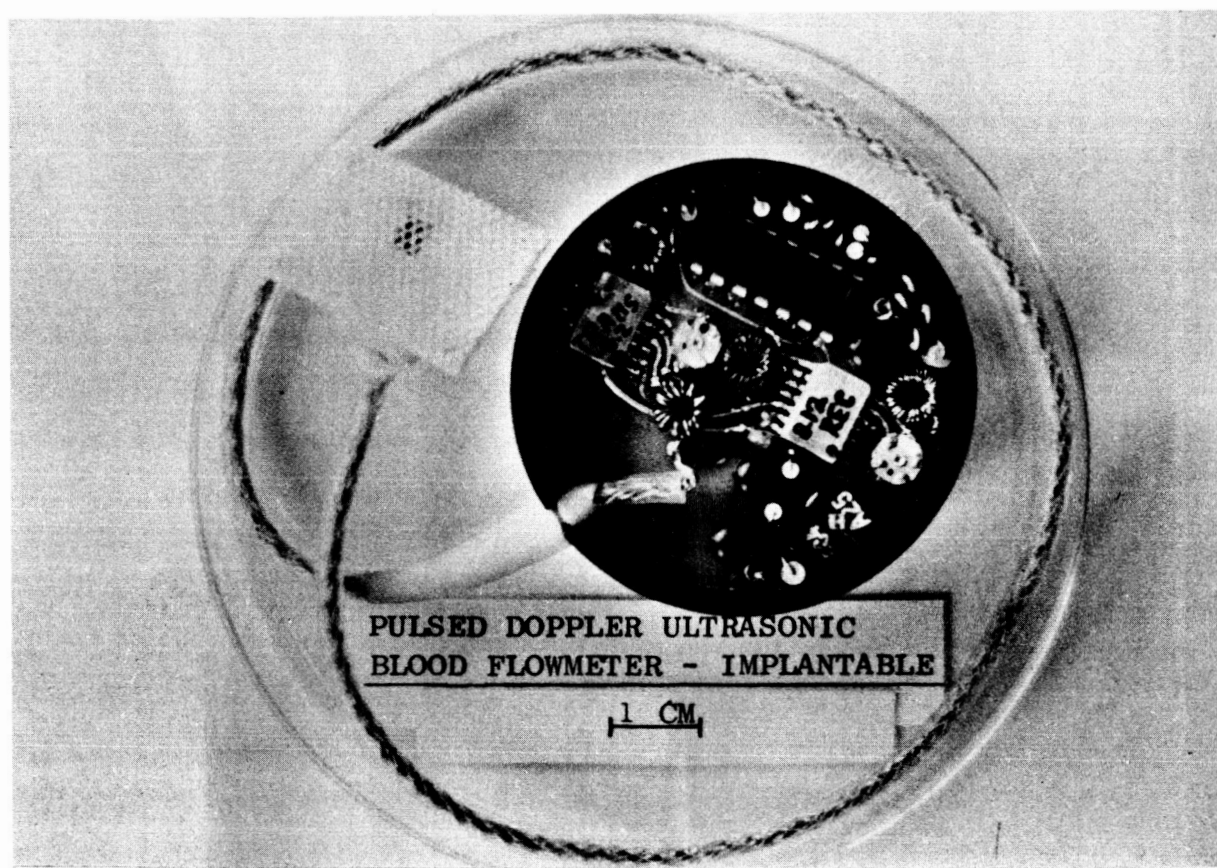


Figure 9.— Prototype implantable pulsed Doppler ultrasonic blood flowmeter, developed by Drs. R. W. Gill and J. D. Meindl, Applied Electronics Laboratory, Stanford University.

# THE RHESUS MONKEY (*Macaca mulatta*) AS A FLIGHT CANDIDATE

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## INTRODUCTION

The rhesus monkey is one of a group of monkeys known as the macaques. The name macaque is derived from the French form of the Portuguese macaquo which is derived from the Congo name for an entirely different type of monkey, so there is some confusion in its origin. The use of the word macaque began about 170 years ago. The great biologist Buffon believed that the Malayan crab eater monkey, the monkey we know now as the Java monkey or *Macaca fascicularis*, was a macaquo from the Congo. This incorrect usage of the word macaque is now permanently fixed. There are many macaques in addition to the rhesus, but the rhesus is probably the best known. Information about the rhesus monkey has already been published in a number of books dedicated to this animal (refs. 1-7).

The rhesus monkey is distributed through the entire northern half of the Indian peninsula. It extends north through the Himalayas and can be found up to elevations of 5000-6000 ft. It extends eastward across Burma into Siam and parts of Indochina, and has even been found in the region of Hong Kong and Fokien, in South China. It extends also to Szechwan in West China and Tche-Li in North China. Throughout the geographical distribution there are six different races represented. The most common race of rhesus found in captivity is the North Indian race. The accepted technical name for the rhesus monkey is *Macaca mulatta*.

## RHESUS MONKEY CHARACTERISTICS

Rhesus monkeys are highly motivated animals and cannot be subdued even by the most unusual circumstances. Despite their aggression and their difficulty of handling, they can be held in a typical primate restraint chair. They react to this restraint by increasing their hydroxysteroid excretion. However, they recover quickly from the effects of this restraint, and the stress symptoms as determined by the hydroxysteroid excretion disappear after about 1 week. This physiological flexibility makes them valuable for experimental studies of the type that would be involved in space. They adapt very readily to a wide variety of foods, and are, in fact, omnivorous. They are also highly intelligent animals, are very well motivated, and will perform all kinds of tasks with training. They have a good sense of balance. Many rhesus monkeys which come into the United States from India are accustomed to living among human beings because it has become the habit of many of them to live in the outskirts of villages and towns and to occupy and live in deserted or even functional temples. They are animals which have a relatively long life, 30 to 40 years. Both the female and male reach sexual maturity at about 3 years, but they do not breed before 4 years, and growth continues for another 7 or 8 years.

The general qualification of rhesus monkeys for space flight may be listed below:

1. There is an impressive body of normative data concerning their anatomy, physiology, and biochemistry.
2. Captive-bred animals are available.
3. Yerkes Primate Center has a breeding colony of rhesus monkeys available designated specially for space studies.
4. They are intelligent animals.
5. They are rugged, and they are mean enough to survive practically anything.

### Physical Characteristics

*Weight*— The weight and size of flight animals in relationship to age are important in considering an animal for space flight. The weight, sitting height, and number of teeth of 44 male and 44 female rhesus monkeys have been listed by Van Wagenen and Catchpole (ref. 8) and are reproduced in tables 1 and 2. Anthropometric parameters were also given by Clark and New (ref. 9) and are reproduced in table 3.

*Length*— Landmarks for each parameter used in tables 1—3 are described below.

Arm 1 (total upper limb length): From thoracic surface of axilla to tip of extended middle fingertip, with arm extended along the body. Arm 2: From tabletop to extended middle fingertip, with both arms extended forward perpendicular to the long axis of the body and with palms together. Arm 3: From thoracic surface of axilla to the tip of the extended fingertip with the arm extended laterally, perpendicular to the long axis of the body. Forearm (elbow to fingertip): From tabletop to extended middle fingertip with the proximal tip of the ulna resting on the tabletop, with the elbow flexed so that the arm is perpendicular to the table top. Hand (wrist to fingertip) (hand length): From tabletop to extended middle fingertip, with carpal joint flexed, and the dorsal carpus resting on tabletop so that the hand is perpendicular to the tabletop.

Foot (foot length): From tuber calcis to the tip of the extended middle toe. Measured in similar manner to the hand.

Tail: From the base to the tip of tail, measured along the volar surface (underside).

Head (total head height): The lower edge of the mandible to the top of the crown.

Lower leg (knee height): From the anterior surface of the femoral condyles to the sole of the foot; hips, knees, and ankles are flexed so that the femur is perpendicular to the tabletop, and the tibia is parallel to the tabletop.

Thigh (length of femur): From the anterior surface of the tibia to the tabletop, with both hip joints flexed so that the legs are perpendicular to the tabletop.



*Width*— Width landmarks for each parameter used in the preceding table are described below.

Foot (foot breadth): Widest point of the metatarsal region.

Hand (hand breadth): Widest point of the metacarpal region.

Chest 3 (transverse chest-diameter): At same level as circumference of chest, with arms extended laterally. Chest 4: At same level as circumference of chest, with arms extended above head.

Shoulders (shoulder breadth): Same level as circumference, with hands at sides.

Waist: Same level as circumference with legs extended.

Hips (hip breadth): Both legs flexed touching each other at knees, measure widest bony prominence (coxofemoral articulation).

Face (face breadth): Area between most lateral prominences of the zygomatic arches.

*Depth*— Depth landmarks used in table 3 are described below.

Chest (chest depth): Same level as circumference of chest.

Pubis: Depth from the ventral surface of the symphysis to the dorsal surface of the sacrum.

Organ weights have been the subject of a number of studies, those published by Kerr et al. (ref. 10) are reproduced in table 4.

### Auditory Thresholds

In studies carried out by Behar et al. (ref. 11) on four monkeys and seven male technicians at the U.S. Army Medical Research Laboratory, Ft. Knox, the human auditory thresholds were found generally slightly lower than those of the monkeys through 4 kHz while above that, the simian thresholds were lower. The rhesus monkey retains good sensitivity up to at least 31.5 kHz.

### Visual Data

Cavonius and Robbins (ref. 12) have tested the visual acuity of five monkeys estimated to be between 3 and 5 years old. They had no refractive errors greater than +1 D, no negative refractive errors, and no significant astigmatism. The ability of the monkeys and man to detect the gap in Landolt ring test objects was tested against background luminances between  $5 \times 10^{-5}$  cd/m<sup>2</sup> and  $5 \times 10^{-3}$  cd/m<sup>2</sup>. At high luminance levels the acuity of human observers was slightly better than that of rhesus. The monkeys had better acuity at scotopic luminance levels. Rhesus monkeys and man had the same threshold for light detection (specified in quanta incident on the retina).

Graham et al. (ref. 13) reported no differences between near and far acuity in the rhesus monkey and found that binocular acuity was superior to monocular acuity.

### Blood

The hematology and blood chemistry of the rhesus monkey are well known and resemble those of man except in a few instances (as shown in tables 5 and 6).

Blood volume has been studied by Bender (ref. 15), using 20 rhesus monkeys weighing from 2.2 to 5.3 kg; blood volumes ranged from 49-71 ml/kg. The results are similar to those given by Freinkel et al. (ref. 16) and Storaasli et al. (ref. 17) for humans. Blood volume was measured using injections of radioactive iodinated human serum albumin and measuring the degree of dilution of radioactivity.

### Serological Taxonomy

The lactic dehydrogenase isoenzymes of rhesus monkeys are closer to chimps and man than those of any other monkey studied. The rhesus monkey is closer to man and apes in (1) chicken antihuman gamma globulin, (2) chicken antihuman ceruloplasmin, (3) rabbit antihuman albumin, (4) rabbit antihuman transferrin, and (5) rabbit antihuman gamma globulin.

A list of antigenic correspondence of primate albumins shows the rhesus monkey to be the closest among the monkeys in relationship to human (table 7).

Other miscellaneous values are given in tables 8 and 9.

### Immunogenetics

Twenty-four immunogenetic systems have now been identified in the rhesus monkey, although they have not all yet been thoroughly elucidated (ref. 20). According to Stone (ref. 21), it is now possible to identify 10 blood group systems, 1 histocompatibility complex which includes a minimum of 4 linked loci, at least 7 serum protein polymorphisms including the allotypes, and about 6 enzyme polymorphisms of the erythrocytes which represent important markers for phylogenetic studies.

Although it is unlikely that each system is located on a different chromosome, if they were, then every rhesus monkey chromosome would have at least one polymorphic marker. In view of the fact that these immunogenetic parameters represent important biological systems, their characterization makes an important contribution to our knowledge of the rhesus monkey.

### Cytogenetics of the Rhesus Monkey

The cytogenetic characteristics of rhesus monkeys have been the subject of considerable study and have been well documented. The diploid number of chromosomes is 42 (ref. 22). At metaphase a distinctive pair of chromosomes can be seen which have a large acromatic region and a linear

satellite. This marked chromosome pair is characteristic of all catarrhine monkeys. It has been noted (ref. 23) that all rhesus monkey autosomes are metacentric with arm ratios of 3.3 or less. The chromosomes have been classified into three main groups: (1) 7 long pairs, (2) 10 medium-sized pairs, and (3) 4 small pairs. Despite this classification the very small Y chromosome was included under (2) presumably because it is the homologue of the X chromosome.

In 1969 Hsu and Benirschke (ref. 24) noted that the rhesus monkey has 40 metacentric or submetacentric autosomes, with the X chromosome being a metacentric and the Y a simple acrocentric. At the Yerkes Center, rhesus monkey chromosomes are karyo-typed simply by arranging them in decreasing order of size.

The A and G banding patterns of the chromosomes of male and female rhesus monkeys have been evaluated and have been found to be identical to those of species of the genera *Papio* and *Cercocebus*. Not many chromosome anomalies have been reported in nonhuman primates, and Farber (refs. 25,26) has recorded normal chromosome complements in two young monkeys with major developmental anomalies. Weiss et al. (ref. 27) have recently described an X-O anomaly in a rhesus monkey with ovarian dysgenesis. This animal had pathological changes which resemble those reported in human phenotypic females with an X-O karyotype (known as Turner's syndrome).

Studies in the Yerkes Center of rhesus monkeys which were long-term radiation survivors have shown only 1 out of about 50 animals which had a morphological chromosomal abnormality — the animal had a normal complement of chromosomes but had a pair of acrocentric chromosomes, which has been interpreted as a deletion of the short arms of this pair of chromosomes.

### Circadian Rhythms

Primates in general and the rhesus monkey in particular respond to changes in periodicity and intensity of light very much like man (ref. 28). This response can be affected by cues other than light and is disturbed by stress. As in man, social interaction may entrain or disturb circadian rhythms. Restraint of the rhesus monkey, frequent taking of samples, and water or food deprivation schedules can seriously affect these rhythms. All physiological systems have a circadian rhythm, under normal conditions, and disturbing factors have to be taken into account in any experimental procedure.

### Respiration

Lung mechanics measurements for the rhesus monkey are presented in table 10 and other respiratory parameters in tables 11-14.

### Cardiovascular Values

**Heart rate**— In reference 39 a heart rate of 100 is given for the rhesus monkey, and this is compared with the rates for a variety of other animals together with rectal temperatures and respiration rates. These are given in table 15.

Stinson and Smith (ref. 40) gave a list of heart rates carried out on six rhesus monkeys at the 6571st Aeromedical Research Laboratory. These animals were unanesthetized and were completely isolated in an environmental chamber for 72 hr in Foringer chairs with free access to food and water. The animals had 10 hr of darkness alternating with 14 hr of light. The heart rate was determined from electrocardiograms monitored with suture electrodes. Immediately after closing the door of the container the heart rate range was highest, 170-225. The mean rate was lowest when the lights were off when the animals were apparently sleeping. Heart rates are listed in table 16.

*Heart sounds*— Hamlin et al. (ref. 41) studied the cardiac cycle in 13 healthy rhesus monkeys, 3–6 years old, with an electrocardiograph and phonocardiograph. The weight of these animals varied from 3 to 14 kg (mean 6.4 kg). The first heart sound started 0.036 sec after onset of Q.R.S. The mean duration was 0.074 sec, with an average of 6.4 vibrations. Systole (mean duration 0.190 sec) was silent in all animals. The second heart sound (mean duration 0.038 sec, average 3.5 vibrations) was lower in magnitude. The period of diastole was silent in nine animals. Average duration of diastole was 0.157 sec.

*Hemodynamic measurements*— Forsyth and Harris (ref. 42) used 21 rhesus monkeys sitting in chairs for the recording of normal hemodynamic measurements and those stressed by being shown a snake. Hemodynamic measurements are presented in table 17.

*Cardiac output and organ blood flow*— Forsyth et al. (ref. 43) studied these parameters in 19 unanesthetized male rhesus monkeys restrained in primate chairs, using radioactively labeled microspheres. Highest blood flow per 100 g of tissue was in the kidney. Intra-arterial catheters were used. The monkeys had normal blood pressures, pulse rates, and catecholamine levels for 9 months after implantation of the catheter.

*Electrocardiography*— The electrocardiography of the rhesus monkey has been studied for nearly 60 years. Malinow (ref. 44) has made an extensive study of this subject and points out that the rhesus monkey ECG can differ from the normal human ECG without this being due to any cardiac pathology. Such changes can be produced by the position of the animals or by the configuration or position of the electrodes; restraint or anesthesia can also affect the ECG, and since rhesus monkeys are hyperexcitable, the autonomic nervous system itself can cause variation. Malinow also points out that the "spread of depolarization and polarization of the myocardium as well as the electric current in the body, may differ in monkeys and in man. Finally, the definition of electrocardiography normality in man has been arrived at by the study of a large number of tracings obtained under standardized conditions and by comparison with extensive clinical, hemodynamic, angiographic and pathological observations which are still lacking in monkeys."

However, Lloyd (ref. 45) found that the ECG's of 17 monkeys were comparable to those of man, findings which were supported in later studies. Experiments with these animals or others, restrained or anesthetized, showed tachycardia with resultant shorter intervals.

*Cerebral angiography*— According to Ryan (ref. 46) the sequence of opacification of the arteries and veins when a cerebral angiogram is performed on a rhesus monkey is similar to that of humans and can be reproduced in a series of studies on a single animal, although there may be a substantial range among a series of rhesus monkeys.

Stahl and Malinow (ref. 32) collected together the published data on the rhesus cardiovascular system up to 1966. This information is reproduced in table 18. Additional data are also shown in tables 19-22.

According to Mason et al. (ref. 55) the mean value of Plasma 17-hydroxycorticosteroids in the rhesus monkey is 34  $\mu\text{g}/100\text{ ml}$  with a range of 19-50  $\mu\text{g}$  (9 male and female rhesus monkeys were used with a weight range of 3-5 kg). See also table 23 for further data on Plasma 17-hydroxycorticosteroids in rhesus monkeys.

#### Corticosteroid Response to Chair Restraint

Mason (ref. 57) has demonstrated that mean 17-OHCS (Plasma 17-hydroxycorticosteroids) levels show a threefold elevation of 1.7 mg/day, compared with a baseline of 0.5 mg/day during the first 3 days after having been placed in a restraining chair. The greatest response is during the first week and its duration varies in individual animals. There were no significant differences in 17-OHCS levels in the same animals when they were housed in cages and during their second month in a chair. These results indicate that there are no appreciable chronic effects of chair restraint upon the pituitary adrenal system.

#### Microscopy of Rhesus Monkey Tissues

The histology, histopathology, and histochemistry of rhesus monkey organs and tissues are widely known. Extensive histological work has been carried out on a number of different organs, and the results published are scattered over a wide range of journals in many languages.

In more recent years, there have been a number of papers on general and enzyme histochemistry and on electron microscopy. This work has been collected together by M. N. Golarz de Bourne and Bourne (ref. 7), and organs and tissues not already studied by other authors were provided by original observations of the authors. Much of the other authors' studies was supplemented by histochemical observations.

It is apparent that the microscopy of rhesus monkey organs and tissues does not differ fundamentally from that of man.

#### Pathology

Pulmonary and gastrointestinal diseases are the leading causes of death in both conditioned and recently imported animals. Bacterial enteritis is responsible not only for considerable mortality, but also considerable morbidity; *Shigella*, *Salmonella*, and enteropathogenic *E. coli* are the most important agents causing this condition. The presence of the organisms, which may live in the gut without causing pathology and then become active with the onset of stress, makes them a potential hazard in primate space flights. This is a problem that must be faced in all monkeys that might be used in space.

Bacterial pneumonia is a serious health problem to the rhesus monkey, although it is most common in recently imported animals. The organisms most commonly implicated are staphylococci, *Streptococcus pneumoniae*, *Hemophilus* sp., and *Kiebsiella* sp.

Among viruses, Herpes virus simiae (B virus) is probably the most serious as far as human contacts are concerned. One study of 1400 rhesus monkeys found oral lesions characteristic of the virus in 2.3 percent of the animals. A survey of 39 laboratory born rhesus showed only one with antibody to B virus. A number of rhesus monkeys in the Yerkes rhesus breeding colony has B virus antibody, but active lesions have not been seen in any of them. Rhesus monkeys may also harbor measles and pox viruses. The latter includes both the Yaba virus and the Yaba-like virus, both of which are transmissible to man (see ref. 58).

The Marburg virus does not appear to occur normally in the rhesus monkey, but the animal can become infected if it is inoculated with the virus. The rhesus monkey is also susceptible to simian hemorrhagic fever.

Mycotic diseases may occur, but are not as common as bacterial and viral diseases. Dermatomycozosis occurs but infrequently in rhesus monkeys. *Candida* is commonly found in the skin, oral cavity, and gastrointestinal tract and has been known to invade the epithelium in the tongue, oral cavity, esophagus, colon, and keratin of the nails. One case of cryptococcosis has been recorded in a rhesus monkey. Mucormycosis has been found more commonly. Rhesus monkeys can be infected with histoplasmosis, but it has not been reported as occurring naturally.

All monkeys carry parasites, and the rhesus monkey is no exception. One of the most common infections is that of lung mites (*Pneumonyssus* sp.), and under normal circumstances, this infection appears to have no clinical effects. If the mites occur in very large numbers, however, it is hard to believe that they do not affect the respiratory competence of the lung. The mites are much more common in wild-born than in laboratory-born animals. Humans can become affected by these mites.

Among the worms that are found in rhesus monkeys are the nodular worm (*Esophagostomum* sp.) ascarids, *Strongyloides*, and hookworms.

A protozoan parasite of muscle (*Sarcocystis*) is found from time to time in rhesus monkey muscle and has been observed in a small number of Yerkes animals. Other protozoan parasites include *Entamoeba histolytica*, *Balantidium coli*, *Toxoplasma organisi*, *Trichomonas* sp., and *Giardia* sp. Mostly these organisms occur without evidence of disease, but they are found occasionally to be associated with a lesion.

Adult cestodes occasionally appear in the rhesus monkey gastrointestinal tract, but do not seem to produce any clinical or histopathological changes.

Trematodes have been found in the gastrointestinal tract, circulatory system, liver, pancreas, and gall-bladder of wild-born nonhuman primates, but since these organisms require an intermediate host, they are not likely to be significant in laboratory-born rhesus monkeys used for space travel.

*Trypanosoma cruzi* has been found in rhesus monkeys, but it is not a common infection.

Noninfectious diseases, e.g., those of the cardiovascular and skeletal systems, have been the subject of study, and Golarz de Bourne and Bourne (ref. 59) have recorded a surprising incidence of skeletal myopathy in the wild-born rhesus monkey which is much less common in laboratory-bred animals.

## Nutrition

*Energy*— The basal heat production for a 4.2 kg monkey (ref. 60) is 207.2 kcal in 24 hr. Another figure which has been calculated is 49 kcal/kg. Various figures have been published for the total energy utilization of rhesus monkeys. According to Robbins and Gavan (ref. 61) who studied the energy utilization of rhesus monkeys varying from 4.0-12.0 kg, the body weight remained stable on an intake of 320 kcal per day. Portman (ref. 62), however, concluded that 100 kcal/kg per day would be a generous allowance for an adult rhesus.

*Protein*— Rhesus monkey milk contains 16 percent of its calories as protein (ref. 63), which means that in this respect it is closer to cow's milk than human milk. Portman (ref. 62) deduces that 3.5 g protein/kg of body weight is adequate for optimum growth in the baby rhesus monkey.

Robbins and Gavan (ref. 61) found that a group of monkeys (4.0-12.1 kg) fed on a diet containing 16.4 percent of protein remained in nitrogen equilibrium on 2.85 g of N per day, this is equivalent to 2.5 g protein/kg body weight/day.

*Unsaturated fats*— Rhesus monkeys maintained growth on 1-2 g of safflower oil per week. This amount represented 1.8 percent of the caloric intake, and it is generally agreed that rhesus monkeys prefer a low-fat diet.

*Vitamins*— The recommended vitamin intakes for rhesus monkeys are listed below (see also ref. 64).

Vitamin A — 400 IU/day

Vitamin D — 25 IU/day

Vitamin K — 0-1 mg/kg body weight. This should be increased if the animals are on antibiotics for any length of time.

Vitamin E — 35 mg mixed natural tocopherols each day, or 0.33-0.83 mg of alpha tocopherol/g of dietary polyunsaturated fatty acids (National Research Council)

Thiamine — 25-30 mg/kg/day

Riboflavin — 41 mg/kg/day

Niacin — 1.6-2.5 mg/kg/day

Pyridoxine — 4.0 mg/day

Pantothenic acid — 3.0 mg calcium pantothenate/day

Biotin — 10 mg/kg/day

Vitamin B<sup>1 2</sup> — Undetermined (8-9 g of fresh liver daily provides an appropriate amount)

Choline — 67 mg/kg/day

Vitamin C — 2.0 mg/kg/day

Calcium — 167 mg/kg/day

Phosphorus — 132 mg/kg/day

Iron — 2.9 mg/kg/day

Iodine — 2.8 mg/kg/day

Water — There is considerable variation in voluntary consumption from day to day. Our rhesus monkeys in cages consume 500-1000 ml/day.

### The Learning Skills of the Rhesus Monkey

According to Zimmerman and Torrey (ref. 65) the rhesus monkey learns well even at birth, and by the time it is 4 to 5 years old it is able to solve an impressive variety of problems and can adapt what it has learned in one situation to another. According to Rumbaugh and Gill (ref. 66) the "fundamental cognitive ability (intelligence) of rhesus in a comparative perspective, as assessed by the Transfer Index method, is among the highest ones measured to date among non-human primates." They go on to point out that great apes are better at the equating and integrating of cross modal stimuli, which is an essential prerequisite for language. It is also indicated that the high cognitive ability of the rhesus monkey is, at least, in part responsible for their adaptability which has enabled them to survive under a wide variety of environmental conditions.

### SUMMARY

The information on the rhesus monkey given in this article is not inclusive. There is a great deal of additional information available, but what has been given here will serve as an indication of the wealth of data available. The munificence of this baseline data emphasizes the claims of the rhesus monkey as a candidate for orbital flight and studies on weightlessness. The preliminary studies carried out so far with Keplerian trajectories indicate that the rhesus monkey adapts to the weightless state.

The rhesus monkey has also played a part in the U.S. space program. Rhesus Macaques were shot into space in rockets between 1948 and 1952, one of them reaching as high as 83 miles. Rhesus monkey "Abel" joined with squirrel monkey "Miss Baker" in 1959 in a suborbital flight. Abel was trained to tap a key every time a red light came on in his capsule. In 1959 rhesus monkeys "Sam" and "Miss Sam" also made rocket flights; they reacted well to the acceleration of takeoff and were able to carry out performance tests during the flight. The experiments have demonstrated that the rhesus monkey can not only survive the stress of being rocketed into space, but can do well during the flight and is able to perform tests during its progress. It has no problems at reentry. There is no doubt that this type of monkey is a highly desirable animal for orbital flight experiments in the shuttle.



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TABLE 1.— MEANS AND STANDARD DEVIATIONS BY AGE (*Macaca mulatta*)  
[Females; Basic Group]

Age, yr		Number of teeth			Weight, kg			Sitting height, mm		
Min.	Max.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
0.0	-0.29	19	0.3	1.00	16	0.437	1.0619	19	191.8	9.14
.030	-.064	16	3.9	1.95	17	.506	.0525	16	209.7	9.75
.065	-.099	17	7.6	1.58	17	.570	.0609	17	215.8	6.98
.100	-.134	16	8.7	1.49	16	.654	.0696	16	229.2	7.19
.135	-.169	15	11.4	3.38	15	.710	.1008	15	238.6	7.95
.170	-.204	17	14.6	3.02	17	.758	.0971	17	245.4	10.32
.205	-.292	27	15.7	1.35	27	.853	.1036	26	256.1	10.75
.293	-.375	20	17.1	1.60	20	1.011	.1397	20	271.8	12.59
.376	-.458	19	18.7	1.66	19	1.140	.1039	18	284.6	10.34
.459	-.541	17	20.0	.0	17	1.286	.1491	17	290.5	13.24
.542	-.624	17	20.0	.0	17	1.409	.1673	17	305.1	13.21
.625	-.707	21	20.0	.0	21	1.526	.1726	21	314.7	13.89
.708	-.790	18	20.0	.0	18	1.667	.1669	18	323.6	14.11
.791	-.873	19	20.0	.0	19	1.699	.2053	19	328.7	15.32
.874	-.956	16	20.1	.25	16	1.846	.1535	15	337.3	15.40
.957	-1.039	19	20.2	.54	19	1.876	.2059	19	343.3	16.74
1.040	-1.122	15	20.5	1.19	15	2.021	.2553	15	347.4	13.91
1.123	-1.205	19	20.9	1.45	19	2.056	.2207	19	353.2	11.94
1.206	-1.288	17	21.5	1.46	17	2.200	.2004	17	359.0	13.49
1.289	-1.371	18	22.2	1.65	18	2.282	.1649	18	364.3	12.40
1.372	-1.454	16	22.9	1.53	16	2.391	.2062	16	369.2	11.65
1.455	-1.586	16	23.8	1.00	16	2.509	.2205	16	375.4	10.88
1.587	-1.752	19	23.8	.50	19	2.659	.2953	19	382.3	11.75
1.753	-1.918	16	24.0	.0	16	2.787	.2275	16	393.8	11.78
1.919	-2.084	16	24.1	.34	16	2.949	.2393	16	400.6	10.76
2.085	-2.250	17	25.2	1.64	17	3.177	.2843	16	407.9	13.18
2.251	-2.416	14	27.9	3.17	14	3.427	.4566	14	419.7	12.89
2.417	-2.582	14	29.9	3.44	15	3.668	.4005	15	428.5	10.42
2.583	-2.748	16	31.5	4.02	16	3.954	.3378	16	437.3	11.52
2.749	-2.914	14	33.9	3.47	14	4.148	.4914	13	440.2	12.36
2.915	-3.166	15	34.1	4.45	16	4.169	.3810	16	446.4	13.30
3.167	-3.500	11	40.5	5.15	11	4.491	.4722	11	453.5	16.53
3.501	-3.830	8	45.1	5.06	8	4.823	.7879	7	472.3	12.40
3.831	-4.166	10	46.6	2.95	10	5.162	.8196	10	472.2	13.16
4.167	-4.500	10	47.5	2.12	10	5.304	.5850	10	473.5	14.02
4.501	-4.833	11	48.2	1.40	11	5.632	.5497	11	480.8	12.23
4.834	-5.166	10	48.0	.0	10	5.669	.6339	10	482.5	16.61
5.167	-5.500	8	49.1	1.25	8	5.909	.8149	8	486.3	19.84
5.501	-5.833	7	50.6	1.51	7	5.939	.5651	7	488.0	14.27
5.834	-6.166	2	51.0	.0	2	6.051	.0	2	484.0	.0
6.167	-6.500	4	50.0	.0	4	5.927	.6433	4	485.0	3.74
6.501	-6.833	3	50.7	.0	3	6.522	.0	2	487.0	.0
6.834	-7.166	0	.0	.0	0	.0	.0	0	.0	.0
7.167	-7.500	1	52.0	.0	1	7.273	.0	1	488.0	.0

TABLE 2.— MEANS AND STANDARD DEVIATIONS BY AGE (*Macaca mulatta*)

[Males; Basic Group]

Age, yr		Number of teeth			Weight, kg			Sitting height, mm		
Min.	Max.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
0.0	—0.029	20	0.3	0.73	16	0.482	0.0545	18	192.5	10.42
	.030— .064	13	5.6	1.45	14	.596	.0706	12	215.3	8.23
	.065— .099	16	7.6	1.63	15	.692	.0560	15	232.2	9.50
	.100— .134	17	10.5	2.70	17	.755	.0735	17	237.9	9.11
	.135— .169	17	12.9	3.08	17	.843	.0954	17	248.2	10.07
	.170— .204	14	14.9	2.18	14	.901	.0970	13	254.9	11.81
	.205— .292	24	16.0	.0	25	.988	.1167	24	266.8	11.26
	.293— .375	21	16.9	1.34	21	1.175	.1346	21	283.5	12.19
	.376— .458	18	18.9	1.71	18	1.321	1.1309	18	297.7	13.12
	.459— .541	17	19.9	.49	17	1.462	.1141	17	308.7	11.14
	.542— .624	21	20.0	.0	21	1.565	.2047	20	317.4	12.85
	.625— .707	21	20.0	.0	22	1.771	.1854	21	326.8	12.80
	.708— .790	23	20.0	.0	23	1.859	.1957	23	338.1	11.97
	.791— .873	23	20.0	.0	23	2.026	.3188	22	345.3	13.97
	.874— .956	21	20.0	.0	22	2.091	.2293	22	351.0	14.61
	.957—1.039	21	20.0	.0	21	2.244	.2063	22	358.3	14.18
	1.040—1.122	22	20.1	.43	22	2.342	.3262	22	365.7	15.57
	1.123—1.205	21	20.9	1.31	21	2.425	.3984	21	369.9	16.59
	1.206—1.288	20	21.8	1.47	21	2.596	.3954	20	376.6	16.71
	1.289—1.371	22	22.3	1.55	23	2.762	.4216	22	381.5	16.54
	1.372—1.454	21	23.0	1.55	21	2.869	.4487	19	386.8	16.21
	1.455—1.586	19	23.5	1.07	19	2.993	.4583	19	395.6	15.73
	1.587—1.752	24	23.8	.56	23	3.122	.4673	23	401.0	16.32
	1.753—1.918	21	24.0	.0	21	3.273	.5197	20	406.5	15.63
	1.919—2.084	19	24.0	.0	21	3.516	.5512	20	417.6	20.96
	2.085—2.250	15	24.9	1.87	16	3.795	.6245	14	428.7	23.17
	2.251—2.416	19	26.3	2.29	19	4.015	.7170	19	437.4	23.44
	2.417—2.582	18	29.3	2.02	18	4.293	.9198	18	445.8	23.75
	2.583—2.748	18	31.9	2.34	17	4.721	1.0128	18	455.1	28.73
	2.749—2.914	16	33.5	1.83	14	4.905	.9475	16	461.9	29.03
	2.915—3.166	19	34.6	2.46	19	5.112	1.1221	19	471.2	29.73
	3.167—3.500	20	37.2	2.57	20	6.004	1.4279	20	493.8	31.50
	3.501—3.830	21	41.0	3.01	21	6.711	1.4433	21	502.8	28.04
	3.831—4.166	20	45.8	2.78	20	7.391	1.4454	20	520.9	31.92
	4.167—4.500	16	47.8	.68	16	8.530	1.4965	16	543.6	24.91
	4.501—4.833	17	49.1	1.69	16	8.762	1.3665	17	541.9	26.38
	4.834—5.566	11	49.6	1.96	11	9.713	1.5117	11	556.8	24.84
	5.167—5.500	5	50.2	2.05	5	11.421	1.4667	5	576.0	24.08
	5.501—5.833	4	50.3	2.06	4	10.056	.6379	4	558.3	33.13
	5.834—6.166	1	50.0	.0	1	8.750	.0	1	537.0	.0
	6.167—6.500	1	50.0	.0	1	8.864	.0	1	536.0	.0
	6.501—6.833	1	52.0	.0	1	8.466	.0	1	540.0	.0
	6.834—7.166	0	.0	.0	0	.0	.0	0	.0	.0
	7.167—7.500	0	.0	.0	0	.0	.0	0	.0	.0

TABLE 3.— ANTHROPOMETRIC PARAMETERS<sup>a</sup> OF *Macaca mulatta*

[36 to 42 Months of Age]

Parameter	Range	Mean	S.D.
<b>Circumference</b>			
Head	257–314	280	17.48
Neck	190–247	217	16.36
Shoulder	377–458	405	25.83
Chest 1	330–437	364	28.87
Chest 2	307–422	351	29.24
Waist	253–313	278	17.89
High thigh	227–320	258	24.51
Mid thigh	200–266	226	16.32
Calf	124–163	139	11.43
Ankle	84–110	95	7.41
Biceps	139–178	157	12.19
Wrist	82–107	87	7.64
<b>Length</b>			
Total length	707–795	748	24.74
Head/buttocks	445–520	474	20.22
Leg	255–348	294	24.76
Arm 1	305–395	347	23.40
Arm 2	380–465	413	24.19
Arm 3	335–400	364	16.89
Forearm	232–266	248	10.01
Hand      ♂ and ♀	100–113	106	4.17
♂	103–113	108	3.94
♀	100–106	103	2.17
Foot	134–153	141	4.94
Tail	222–294	255	19.13
Head	84–105	89	5.73
Lower leg	174–211	192	9.43
Thigh	187–211	198	8.19
<b>Width</b>			
Foot	42–59	47	4.77
Hand	34–49	42	4.19
Chest 3	61–87	75	7.84
Chest 4	60–81	69	5.66
Shoulder	124–167	143	10.96
Waist	77–101	88	7.06
Hip	103–127	113	6.35
Face	70–88	77	4.80
<b>Depth</b>			
Chest 5	93–114	100	6.47
Pubis	53–77	62	7.54
Weight in grams:	4410–5700	5185.8	360.9

<sup>a</sup>Expressed in millimeters. Only those parameters that showed a significant difference between sexes are so distinguished.

TABLE 4.— ORGAN WEIGHTS OF ADULT RHESUS MONKEYS

Organ	Adult males ( <i>N</i> = 27)						Adult females ( <i>N</i> = 15)					
	Organ weight			Percentage body weight			Organ weight			Percentage body weight		
	Mean	S.D.		Mean	S.D.		Mean	S.D.		Mean	S.D.	
Total body weight, kg	6.186	1.775		1.38	0.43		5.59	1.76		1.61	0.59	
Brain, g	87.14	12.46		.45	.12		82.19	15.19		.39	.091	
Heart, g	27.42	9.70		.92	.37		22.13	8.22		1.00	.408	
Lungs, g	51.85	15.59		.079	.041		51.92	14.28		.079	.045	
Spleen, g	4.620	2.327		2.39	.556		4.107	1.805		2.56	.93	
Liver, g	144.89	48.63		.026	.013		138.16	46.29		.040	.021	
Adrenals, g	1.48	.56		.399	.126		2.14	1.19		.477	.249	
Kidneys, g	24.14	6.44		.020	.008		25.45	11.19		.024	.018	
Thyroid, g	1.253	.415					1.51	1.70				



TABLE 5.— HEMATOLOGY

	Rhesus monkey	Man
Blood count		
RBC	3.56–6.95 million	4.5–5.5 million
WBC	2.5–26.7 thousand	6.0–10.0 thousand
Hemoglobin	8.8–16.5 g/100 ml	14.0–16.0 g/100 ml
Leukocytes		
Neutrophils	5.1–88.0 percent	65–75 percent
Lymphocytes	8.0–92.0 percent	20–30 percent
Monocytes	0–11.0 percent	1.0–2.0 percent
Eosinophils	0–14.0 percent	2.0–3.0 percent
Basophils	0–0.6 percent	0.5 percent
Blood chemistry		
Total protein	4.9–9.3 g/100 ml	6.0–8.0 g/100 ml
Albumin	2.8–5.2 g/100 ml	3.5–5.6 g/100 ml
Globulin	1.2–5.8 g/100 ml	1.3–3.2 g/100 ml
SGOT	16–97 S.F. units	8–40 S.F. units
SGPT	0–68 S.F. units	5–35 S.F. units
LDH	393–713 units	100–350 units
Glucose	46–178 mg/100 ml	80–120 mg/100 ml
BUN	8–40 mg/100 ml	8–20 mg/100 ml
Calcium	6.9–13.0 mEq/l	9.5–11.5 mEq/l
Phosphorus	3.1–7.1 mg/100 ml	2.5 mg/100 ml
Sodium	102–166 mEq/l	138–146 mEq/l
Potassium	2.3–6.7 mEq/l	3.8–5.1 mEq/l
Chloride	84–126 mEq/l	95–106 mEq/l
CO <sub>2</sub>	10–16 mEq/l	20–29 mEq/l
Creatinine	0.1–2.8 mg/100 ml	0.8–1.3 mg/100 ml
Uric acid	0.1–1.4 mg/100 ml	2.6 mg/100 ml
Cholesterol	152–170 mg/100 ml	150–217 mg/100 ml

TABLE 6.— BLOOD SUGAR AND INSULIN<sup>a,b</sup>

Value	Blood sugar, mg/100 ml	Insulin M, g/ml
Mean	82.2	1.19
Range	69 - 152	Less than 1.0 - 7.2
Standard error or deviation	±16	±1.41

<sup>a</sup>Values taken from 52 male rhesus monkeys (4-5 kg).

<sup>b</sup>Reproduced from Wherry et al. (ref. 14).

TABLE 7.— CROSS REACTION<sup>a</sup>

Primate	Percent	Primate	Percent
Homo	100	Green monkey	76
Gorilla	98	Spider monkey	65
Chimpanzee	96	Squirrel monkey	62
Gibbon	82	Capuchin monkey	52
Rhesus	82	Common lemur	37
Colobus	80	Tree shrew	36
Baboon	78	Galago (bush baby)	31
Mangabey	78	Domestic pig	7
Owl monkey	77		

<sup>a</sup>Taken from reference 18.

TABLE 8.— BLOOD CLOTTING IN VARIOUS PRIMATES INCLUDING THE RHESUS MONKEY<sup>a,b</sup>

Species	Number of animals	Prothrombin and proconvertin, percent	Quick test, sec	Partial Thromboplastin test, sec	Fibrinogen, mg/100 ml	Contact activation		Platelets, $\times 10^3/\text{mm}^3$	Hematocrit, percent
						Without kaolin, percent	With kaolin, percent		
<i>L. fulvus</i> ; <i>L. catta</i>	11	100±5	12.6±0.3	37.6±2.9	306±16	94±18	108±10	508±52	49.5±1.3
<i>M. mulatta</i> (Rhesus)	10	172±8	12.0±0.3	47.2±1.1	310±18	40±11	103±10	495±35	41.2±1.1
<i>M. nemestrina</i>	11	153±8	12.6±0.3	46.8±1.3	338±26	7±4	42±10	478±33	44.8±1.0
<i>M. fuscata</i>	5	142±7	11.6±0.2	44.4±0.9	198±25	116±56	86±14	344±32	46.0±0.8
<i>M. speciosa</i>	3	136±10	10.9±0.4	44.7±1.1	325±72	32±15	197±27	543±137	41.6±3.1
<i>M. radiata</i>	3	152±16	12.6±0.2	44.2±0.1	272±79	1.3±0.4	17±2	518±100	46.9±1.3
<i>C. niger</i>	6	120±17	14.0±0.6	49.1±0.9	281±17	0.9±0.0	4±1	367±42	42.8±1.3

<sup>a</sup>From Seaman and Malinow (ref. 19).<sup>b</sup>Values represent mean and S.D.TABLE 9.— RHESUS MONKEY CEREBROSPINAL FLUID CHEMISTRY VALUES<sup>a</sup>

Determination	Males		Females	
	Mean value	Range	Mean value	Range
Sodium, mEq/l	153.2	145–157	153.5	151–158
Potassium, mEq/l	2.6	2.4–3.0	2.7	2.5–2.9
Calcium, mEq/l	2.3	2.2–2.5	2.5	2.4–2.7
Chloride, mEq/l	131.8	129–134	133.5	131–137
Total protein, mg percent	41.7	35–50	37.5	31–47
SGOT, S.E. units	21.0	15–29	19.5	16–24
SGPT, S.E. units	12.3	8–16	11.7	6–18
LDH, Berger-Broida units	18.0	0–35	24.0	0–35

<sup>a</sup>From Turbyfill et al. (ref. 20).

TABLE 10.— MEASUREMENT OF LUNG MECHANICS IN RHESUS MONKEY, SHOWING MEANS FOR EACH SEX AND TOTAL GROUP MEANS<sup>a,b</sup>

Animals	Weight, kg	V <sub>t</sub> , ml	f, cycles/min	RMV, ml/min	DEDC, percent	V <sub>tp</sub> , cm/ H <sub>2</sub> O	C <sub>dyn</sub> (I), ml/cm H <sub>2</sub> O	Rl(i)	Rl(e)	Rl(i) Rl(e), percent	Rl, cmH <sub>2</sub> O/ ml/sec
								cmH <sub>2</sub> O/ml/sec			
Males											
Mean	3.48	38.9	38	1441	54	3.9	10.30	0.0015	0.029	55	0.022
±S.D.	.592	10.64	5.8	283	3.7	.56	2.86	.008	.014	18.6	.011
Females											
Mean	3.33	46.0	40	1820	55	4.3	11.54	.014	.028	54	.020
±S.D.	.38	8.96	9.7	549	3.6	1.21	3.96	.007	.010	24.1	.008
Total											
Mean	3.40	42.5	39	1630	54	4.1	10.92	.014	.028	54	.021
±S.D.	.49	10.19	7.7	465	3.6	.93	3.39	.007	.011	20.8	.009

<sup>a</sup>From Binns et al. (ref. 29).

<sup>b</sup>Vt, tidal volume; f, respiration ratio; RMV, respiratory minute volume; DEDC, percentage of duration of the complete respiratory cycle; Vtp, pressure change between end tidal volume at inspiration and expiration; Cdyn(I), dynamic lung compliance; Rl(I), pulmonary resistance during inspiration; Rl(e), pulmonary resistance during expiration; Rl, average pulmonary resistance.

TABLE 11.— RESPIRATORY QUOTIENTS OF RHESUS MONKEYS IN THE POST-ABSORPTIVE STATE<sup>a</sup>

Animal number <sup>b,c</sup>	Weight, kg	Age, years	Respiratory quotient average	S.D.
Females				
1	6.5	6.4	0.88	
2	5.7	4.5	.69	
3	6.2	4.6	.83	
4	6.7	4.3	.89	
5	3.9	6.8	.91	
6	5.5	4.7	.74	
7	5.1	3.5	.75	
8	4.4	2.8	.77	
9	3.4	2.6	.68	
10	4.1	2.3	.77	
11	3.6	1.8	.73	
12	3.2	1.7	.89	
13	2.1	1.4	.76	
14	3.0	1.7	.79	
15	1.4	.6	.84	
			Avg. 0.80	0.08
Males				
16	6.4	3.4	0.81	
17	7.9	3.2	.75	
18	4.0	2.5	.65	
19	3.9	2.7	.89	
20	3.7	2.0	.82	
21	3.3	1.8	.78	
22	2.9	1.6	.84	
23	2.5	1.3	.87	
24	2.1	.8	.79	
25	2.0	.8	.84	
26	2.0	.8	.81	
27	1.6	.8	.73	
			Avg. 0.80	0.07

<sup>a</sup>From Robbins and Gavan (ref. 30).

<sup>b</sup>Twenty-seven rhesus monkeys were used ranging from infancy to middle age. They were fed Purina Monkey Chow as a routine diet.

<sup>c</sup>Animals 1 through 6 are wild-born.

TABLE 12.— THE RESPIRATORY METABOLISM OF NORMAL ANIMALS<sup>a</sup>

Animal	Sex	Age	Weight	O <sub>2</sub> /hr:I.	Respiratory quotient	Cal/kg, 24 hr	Cal/m <sup>2</sup> , 24 hr	Chamber temperature
Rhesus	M	A <sup>b</sup>	3.70	1.70	0.81	53.1	701	22.5
Rhesus	F	A	4.35	1.71	.84	45.8	638	23.8
Rhesus	F	A	8.10	2.56	.78	36.2	621	23.3
Rhesus	F	A	8.10	2.68	.78	37.9	650	23.2
Average for rhesus							653	
Mangabey	M	I <sup>c</sup>	3.40	1.49	0.80	50.5	649	22.7
Mangabey	M	I	3.40	1.47	.85	50.5	649	23.8
Mangabey	M	I	3.40	1.48	.79	50.5	642	24.0
Mangabey	M	I	4.10	1.69	.81	47.6	650	23.0
Mangabey	M	I	4.10	1.72	.77	48.0	657	24.0
Mangabey	M	I	4.10	1.75	.80	49.2	673	23.3
Average for mangabey							653	
Baboon	M	A	5.30	2.45	0.78	53.0	789	23.3
Baboon	M	A	5.80	2.53	.77	49.7	762	23.4
Baboon	M	A	5.80	2.54	.78	50.2	770	23.5
Baboon	M	A	7.60	2.91	.76	43.7	735	22.5
Baboon	M	A	7.60	2.99	.79	45.2	761	22.4
Baboon	M	A	7.60	2.74	.75	41.0	690	24.3
Baboon	M	A	7.60	2.88	.75	43.1	728	23.8
Average for baboon							748	
Gibbon	M	I	1.90	1.15	0.79	69.6	658	23.4
Gibbon	M	I	1.90	1.02	.79	61.7	583	24.5
Gibbon	M	I	1.90	1.05	.79	63.5	600	25.7
Average for gibbon							613	
Orangutan	F	A	16.20	5.01	0.77	35.4	793	22.9
Orangutan	F	A	16.20	4.98	.78	35.2	791	23.2
Orangutan	F	A	16.20	4.92	.78	34.8	781	24.2
Average for orangutan							788	

<sup>a</sup>From Bruhn (ref. 31).<sup>b</sup>A means an adult monkey.<sup>c</sup>I means an infant monkey.

TABLE 13.— BLOOD AND RESPIRATORY GAS CONSTANTS<sup>a</sup>

Normal value	Reference number	Normal value	Reference number
<b>Minute volume</b>		<b>Respiratory flow resistance</b>	
1650 ml/min	33	8.6 cm H <sub>2</sub> O/(1/sec)	34
700 ml/min	34	4.4–14.2 cm H <sub>2</sub> O/(1/sec)	34
260–1340 ml/min	34		
3860 ml/m <sup>2</sup> ·min	35	<b>Work of breathing</b>	
2860–4960 ml/m <sup>2</sup> ·m	35	817·g-cm/min	34
860 ml/min	36	223–1418 g-cm/min	34
310–1410 ml/min	36		
1791±369 ml/min	37	<b>Respiratory quotient</b>	
		0.77±0.03	37
<b>Vital capacity</b>		<b>Arterial-venous oxygen difference</b>	
230–580 ml		5.25±0.05 vol. percent	37
<b>Tidal volume</b>			
42 ml	33	<b>Arterial pH</b>	
20 ml	34	7.432±0.072	37
9–29 ml	34		
21.0 ml	36	<b>Venous pH</b>	
9.8–29.0 ml	36	7.436±0.048	37
43.5±8.1 ml	37		
<b>Functional residual capacity</b>		<b>Total arterial plasma CO<sub>2</sub> content</b>	
87.5 ml	34	29.2±6.1 mEq/l	37
61–115 ml	34	<b>Whole blood arterial buffer base</b>	
		60.6±8.2 mEq/l	37
<b>Dead space</b>			
12.6±7.1 ml	37	<b>Arterial O<sub>2</sub> tension</b>	
		65 mm Hg	33
<b>Lung compliance</b>			
12.3 ml/cm H <sub>2</sub> O	34	<b>Arterial CO<sub>2</sub> content</b>	
7.1–20.2 ml/cm H <sub>2</sub> O	34	44.2 vol. percent	33
<b>Distensibility</b>			
0.12/cm	34	<b>Arterial CO<sub>2</sub> tension</b>	
0.08–0.22/cm	34	31 mm Hg	33
		42.9±8.3 mm Hg	37

<sup>a</sup>From Stahl and Malinow (ref. 32).

TABLE 14.— RESPIRATORY BLOOD GASES AND pH<sup>a</sup>

	Weight, kg	PaO <sub>2</sub> , mm Hg <sup>b</sup>	PaCO <sub>2</sub> , mm Hg <sup>b</sup>	pH	Base excess, mEq/l <sup>c</sup>
Rhesus monkeys (6)					
Mean	5.9	100.8	42.6 <sup>d</sup>	7.46	4.8
±S.D.	±0.5	±7.0	±1.0	±0.04	±1.8
Cynomolgus monkeys (6)					
Mean	5.3	100.7	38.8 <sup>d</sup>	7.47	4.1
±S.D.	±1.4	±4.2	±2.7	±0.02	±1.7

<sup>a</sup>From Munson et al. (ref. 38).<sup>b</sup>PaO<sub>2</sub>, arterial oxygen tension; PaCO<sub>2</sub>, arterial carbon dioxide tension.<sup>c</sup>Calculated value, based on 15 g hemoglobin concentration.<sup>d</sup>P < 0.01.TABLE 15.— THE AVERAGE NORMAL TEMPERATURE AND PULSE RATE OF SOME COMMON LABORATORY ANIMALS<sup>a</sup>

Animal	Rectal temperature, °C	Rectal temperature, °F	Rate/min	
			Pulse	Respiration
Cat	38.7	101.6	130	24
Dog	38.6	101.4	95	14
Frog	8.9–17.2	48.2–62.9	80	12
Fowl	41.6	106.8	140	12
Guinea pig	38.6	101.48	150	80
Goat	40.0	104.0	75	16
Horse	37.9	100.2	38	11
Mouse	37.4	99.3	600	163
Monkey, Rhesus	38.4	101.1	100	19
Ox	38.8	101.8	60	15
Pigeon	40.9	105.6	136	30
Rabbit	38.7	101.6	135	55
Rat	37.5	99.5	300	210
Hamster	36–38	98–101	450	74

<sup>a</sup>From reference 39.



TABLE 16.— HEART RATE AT EIGHT-HOUR INTERVALS<sup>a</sup>

Hour	Chamber lights	Mean	S.D.	Range
0	On	193	20.3	170–225
8	On	143	21.5	105–175
16	Off	132	13.1	120–160
24	On	147	21.0	115–175
32	On	147	20.6	105–170
40	Off	131	16.7	110–155
48	On	150	11.9	130–165
56	On	139	29.6	95–165
64	Off	128	15.5	95–140
72	On	143	30.6	100–195

<sup>a</sup>From reference 40.TABLE 17.— HEMODYNAMIC MEASUREMENTS IN THE FIVE CONTROL, THREE SNAKE-STRESSED, AND TWO AVOIDANCE-STRESSED MONKEYS<sup>a</sup>

Measurement	Animal	Before stress		During stress	
		Mean	S.D.	Mean	S.D.
Systolic arterial pressure, mm·Hg	C <sup>b</sup>	145	16	145	12
	SS	149	14	139	15
	AS	153	12	168	15
Diastolic arterial pressure, mm Hg	C	84	11	84	10
	SS	92	10	86	12
	AS	94	7	104	11
Mean arterial pressure, mm Hg <sup>c</sup>	C	113	13	112	12
	SS	120	11	109	14
	AS	124	9	136	11
Cardiac output, l/min	C	1.31	.3	1.26	.2
	SS	1.19	.2	1.68	.1
	AS	1.09	.2	1.51	.2
Total peripheral resistance, mm Hg/l/min <sup>d</sup>	C	88	15	86	14
	SS	99	18	63	16
	AS	116	24	95	21
Pulse rate, beats/min	C	174	13	178	14
	SS	179	16	224	22
	AS	168	19	208	26
Stroke volume, ml	C	7.5	.9	7.1	.6
	SS	7.2	1.4	7.5	1.1
	AS	6.7	1.3	7.2	1.4

<sup>a</sup>From reference 42.<sup>b</sup>C, 5 control; SS, 3 snake-stressed; AS, 2 avoidance-stressed monkeys.<sup>c</sup>Electronically integrated.<sup>d</sup>Hg/l/min = (mean arterial pressure – mean right atrial pressure)/cardiac output.

TABLE 18.— CARDIOVASCULAR SYSTEM<sup>a</sup>

Normal value	Reference number	Comments
<b>Heart rate</b>		
168±30/min	35	Mean and S.D. in 8 animals with mean weight of 7.6 kg. Pentobarbital anesthesia
174±18/min	37	Mean and S.D. in 14 animals with mean weight of 5.3 kg. Phencyclidine analgesia
257±31/min	47	Study of 351 animals (mostly females) with mean weight of 4.9±1.7 kg. No anesthesia. Mean±S.D. shown
<b>Cardiac output</b>		
1800±700 ml/m <sup>2</sup> min (Fick)	35	See above
1070±300 ml/min (Fick)	37	See above
980±320 ml/min (dye)		
90–200 ml/kg·min	37	Total reported literature and experimental range of cardiac output per kg
<b>Cardiac stroke volume</b>		
10.7±3.0 ml/m <sup>2</sup>	35	See above
5.8±2.4 ml (Fick)	37	Mean and S.D. for 8 animals with mean weight of 5–6 kg. Phencyclidine analgesia
<b>Total peripheral resistance</b>		
11,200±3700 dyn·sec/cm <sup>5</sup>	35	See above
<b>Pulmonary vascular resistance</b>		
849±376 dyn·sec/cm <sup>5</sup>	35	See above
<b>Time-tension index heart</b>		
3560±930 mm Hg·syst. sec/min	35	See above
<b>Systolic ejection rate index</b>		
55.0±21.2 ml/syst. sec·m <sup>2</sup>	35	See above
<b>Left ventricular work rate</b>		
2.48±0.96 g·m/m <sup>2</sup> ·beat	35	See above
<b>Left ventricular stroke work index</b>		
14.3±2.0 g·m/m <sup>2</sup> ·beat	35	See above
<b>Cardiac cycle intervals</b>		
0.035±0.004 QRS(s)	48	Study of 15 normal adult animals, without anesthesia. Mean±S.D. shown
0.07±0.01 PR (s)	47	See above
0.03±0.007 QRS (s)	47	
0.14±0.01 QT (s)	47	

<sup>a</sup>From reference 32.

TABLE 19.— NORMAL VALUES OF VECTORCARDIOGRAMS IN  
FIFTEEN RHESUS MONKEYS<sup>a</sup>

Measurement	Horizontal plane	Left sagittal plane	Frontal plane
Magnitude, maximum QRS vector, mV	1.61±0.45 (1.10–2.46)	1.65±0.30 (1.28–2.30)	1.71±0.55 (0.93–2.94)
Angle, maximum QRS vector, deg	307±54 (227–31)	53±50 (337–126)	65±55 (21–211)
Angle, half-area QRS vector, deg	335±35 (243–33)	75±31 (348–127)	48±27 (349–101)
Magnitude, T vector, mV	0.46±0.21 (0.16–0.89)	0.46±0.12 (0.32–0.77)	0.48±0.17 (0.29–0.98)
Angle, T vector, deg	45±14 (25–72)	136±18 (85–156)	42±16 (11–70)
Angle between maximum QRS and T vectors, deg	98±52 (32–172)	89±51 (30–172)	32±62 (1–176)
Angle between half-area QRS and T vectors, deg	70±29 (33–149)	61±29 (25–133)	18±26 (0–66)
Direction of QRS inscription			
Counterclockwise	14	15	5
Clockwise	0	0	4
Figure of eight	1	0	6

<sup>a</sup>From Bristow and Malinow (ref. 48). Shown as mean±S.D. with range in parentheses.

TABLE 20.— FLUID VOLUMES IN RHESUS MONKEYS

Normal value	Reference number	Comments
<b>Blood volume</b>		
54.1 ml/kg	36	Based on 18 animals of unknown mean weight (from red cell + plasma volumes)
44.3–66.6 ml/kg	36	
54–77 ml/kg	49	Based on about 50 animals with weight range of 3–7 kg (from red cell + plasma volumes)
<b>Plasma volume</b>		
36.4 ml/kg	36	T-1824 dye determination in 18 animals of unknown mean weight
30.0–48.4 ml/kg	36	
36–47 ml/kg	49	T-1824 dye determination in the group cited above
<b>Red cell volume</b>		
17.7 ml/kg	36	$^{32}\text{P}$ red cell tag studies in 16 animals of unstated mean weight
14.3–20.0 ml/kg	36	
17.7±1.7 ml/kg	49	$^{32}\text{P}$ red cell tag studies in 18 animals of 3.4–7.1 kg
<b>Total body water</b>		
695 ml/kg	50	Mean and range of antipyrine dilution in 5 animals
628–721 ml/kg	50	
691 ml/kg	50	Mean and range for desiccation in 7 animals
650–720 ml/kg	50	
62–72 percent	51	Antipyrine dilution in animals of 2.85–3.64 kg.
66–71 percent	51	Desiccation in same group
<b>Extracellular fluid</b>		
208 ml/kg	50	Thiocyanate space in 16 animals of unstated weight
121–295 ml/kg	50	

TABLE 21.— RENAL FUNCTION PARAMETERS IN RHESUS MONKEYS<sup>a</sup>

Normal value	Reference number	Comments
Inulin clearance 1.96 ml/kg·min 1.18–3.03 ml/kg·min	52	Mean and range based on 40 observations in 7 animals weighing 4.1–11.0 kg
Creatinine clearance 3.08 ml/kg·min 1.72–5.22 ml/kg·min	52	Mean and range based on 29 observations in above group
PAH clearance 8.06 ml/kg·min 6.71–10.90 ml/kg·min	52	Mean and range based on 13 observations in above group
Renal plasma flow 11.9 ml/kg·min 9.5–14.4 ml/kg·min	53	Mean and range in studies on 8 unanesthetized animals
Glomerular filtration rate 2.07 ml/kg·min 0.93–3.30 ml/kg·min	53	See above
Urine formation rate 70–80 ml/kg·day	50	Unknown number of animals with mean weight of 12 kg

<sup>a</sup>From reference 32.

TABLE 22.—COMPARATIVE URETERAL PHYSIOLOGY<sup>a</sup>

Animal	Peristalsis, contraction/min	Amplitude, mm Hg	Baseline, mm Hg
Dog (Boyarsky)	2–20(9) <sup>b</sup>	10–15(13)	0–10(10)
(Deluca)	6–8	15–37	0–10
Man (Weinberg)	1–8	2–14	1–6
(Edmond)	2–6	11–59	
(Sala and Rubi)	1–9(4)	1–30(13)	1–20(9)
Monkey			
Rhesus ( <i>M. mulatta</i> )	1–10(3)	1–21(7)	1–10(5)
Stumptail ( <i>M. arctoides</i> )	1–11(3)	1–21(6)	2–9(5)

<sup>a</sup>Data reported on ureteral physiology is reprinted through the permission of Williams and Wilkins Co., Baltimore, Maryland. See reference 54.

<sup>b</sup>Numbers in parentheses indicate number of observations.

TABLE 23.—PLASMA 17-HYDROXYCORTICOSTEROIDS  
IN YOUNG RHESUS MONKEYS<sup>a</sup>

Number of animals	Time, days	Mean value, μg/100 ml
14	2	48±4
10	9	46±6
9 <sup>b</sup>		39±3

<sup>a</sup>From Wolf and Bowman (ref. 56).

<sup>b</sup>Adult animals

## THE CHIMPANZEE AS A FLIGHT CANDIDATE

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Today's comments will be directed to the chimpanzee as a model for cardiovascular studies related to space flight, but some general comments will also be made on the chimpanzee as a flight subject.

During the past 18 months, cardiovascular research teams from Howard University, Ames Research Center, NASA, and The University of Texas Medical School in Galveston have brought their expertise and previous experience in instrumenting chimpanzees to the Yerkes Regional Primate Research Center to further explore the feasibility of monitoring cardiac performance in instrumented chimpanzees and to investigate the performance and problems involved in using implantable, multichannel, radiotelemetry systems. Some of the characteristics that make the chimpanzee an attractive animal model (anatomy, size, intelligence, and durability) also create some very unique problems. The universally recognized problems of availability and expensive maintenance, combined with the often underestimated problems associated with routine housing, husbandry, restraint, and medical management, severely limit the available avenues of approach. For these reasons, the surgical implantation of radiotelemetry devices for monitoring cardiodynamics in the chimpanzee is wisely conducted as a team effort in an institution that specializes in this animal model. The Yerkes contribution included the acquisition and preoperative screening of surgical candidates, the initial physical and chemical restraint, and the gas anesthesia during open chest surgery. A surgical theater and support personnel for sterile open chest surgery was provided, as was the intensive and long range postoperative care. Finally we had to provide uncomplicated and predictable postoperative access to instrumented chimpanzees for data collection. The time is inadequate to detail all of these supportive responsibilities, but I would like to highlight areas we feel worthy of mention. There are a number of Yerkes publications that describe routine husbandry, restraint, surgery, and medical management of the chimpanzee, and Sandler (ref. 1) and Stone (ref. 2) have published their experiences instrumenting chimpanzees.

The surgical subjects were initially immobilized with 20 mg/kg body weight of ketamine HCl, and atropine was administered at the same time. Clipping, shaving, surgical scrub, intravenous catheter placement for fluids, and, if requested, presurgical administration of xylocaine were all performed under ketamine anesthesia. The chimp was then transferred to the surgical theater, intubated, and stabilized on a 60:40 nitrous oxide and oxygen mixture with 0.5-1.5 percent halothane introduced. Surgical monitoring equipment included ECG, esophageal stethoscope, pressure cuff, and sphygmomanometer with transcutaneous doppler rather than a stethoscope for monitoring, and blood gas analysis was available. For the adult chimps (40-53 kg) the combination sphygmomanometer and transcutaneous doppler was usually adequate for monitoring the low blood pressures required for the surgical manipulations. However, this technique proved inadequate with smaller subjects (20 kg), and I would recommend the routine use of an arterial catheter and transducer for a continuous readout of the blood pressures. Although it requires an additional 20-min effort, the advantages of a continuous, more accurate readout of the very low pressures

certainly justify the procedure. A three-way stop clock at the site also facilitates the retrieval of arterial blood samples for blood gas analysis. A word of caution here would be to be sure the heparin solution used to flush the catheter is not so concentrated that repeated use during a 4-hr procedure will cause bleeding problems later.

Once the animal was stabilized on the gas anesthesia and all monitoring equipment was functioning, the animal received a final prep, and from this point sterile technique was employed. The chest was usually open 3-4 hr, and the chimp was ventilated by manual bagging. A chest drainage tube was placed during the closure, and the chest was evacuated 3-4 hr postoperatively. Before the chest tube was removed, radiographs were taken to confirm complete expansion of the lung and to ascertain that there was no excess fluid or air in the thorax. During the chest drainage and chest radiography, the animals were immobilized with nitrous oxide or ketamine HCl. To shorten the recovery period, an intravenous ketamine drip was used to radiograph and transport the animals to a small recovery cage. The animals were confined for 2 weeks postoperatively in a small enclosure that had a built-in restraining device. They received therapeutic doses of sodium methicillin, lincomycin, ampicillin, and sodium colistimethate 7 days postoperatively. A 10-day postoperative profile included a complete CBC, blood chemistry, and chest radiographs. The animals were returned to their home cage 2 weeks postoperatively.

In May 1973, the first series of five adult animals (40-53 kg) was operated. Two animals experienced ventricular fibrillation during the surgery, and attempts to revive the animals were unsuccessful. Of the three successfully instrumented animals, there were no significant postoperative complications and, based on subsequent routine surveys, they are in excellent condition to date.

The animals' instrumentation included a receiving antennae in the posterior gutter of the thorax that was used for subsequent recharging of the power source. The charging procedure required close contact for several hours, and this necessitated the fitting and use of a nylon mesh jacket for the chimp. One animal tolerated the nylon mesh and chain link jacket very well for an 8-hr trial period. Further modification of the jacket in the form of leg straps may be necessary to improve antennae and charger contact and facilitate energy transfer. This concept may certainly be feasible in some select chimpanzees.

A series of three animals (20-25 kg) was instrumented in May 1974. The major difference between this and the earlier experiment was that these animals were hard-wired, and we experienced considerable postoperative complications which resulted in the eventual euthanasia of two of these chimps 2-1/2 and 3 months after instrumentation. The major problem seemed to be the animals' inability to cope with contaminated lead wires buried in subcutaneous pockets for the purpose of exteriorizing and collecting data at a later date. Sterile techniques were of necessity compromised once the chest was closed and the tunnel and subcutaneous pocket were being established. There were no problems with the animals bothering these subcutaneous pockets on their backs.

Despite intensive efforts at irrigation, topical decontamination, reestablishing a subcutaneous pocket in a new site with the lead wires buried in silastic, and rather heroic doses of systemic antibiotics, the infection could not be controlled. The lead wires seemed to act as a wick to the chest. One animal experienced cerebral and lower limb emboli which led to a gangrenous limb and the necessary euthanasia. Sandler (ref. 1) reported similar problems in dogs with hard-wire instrumentation.



The other chimp healed well after surgical instrumentation but experienced a wound contamination and clinical deterioration after the first exteriorization procedure for data collection. Similar efforts to control the infection were futile, and these animals were euthanized after the development of empyema.

Blood cultures revealed a beta hemolytic *Streptococcus* and *Staphylococcus aureus* septicemia in both animals.

And now some general comments on the chimpanzee as a flight candidate. Because of his phylogenetic closeness to man, the chimpanzee is always a contender for comparative biomedical research, and a precedent was set in 1961 for his use in space research ("Ham" and "Enos" — the first chimps used in suborbital flights by the USA in 1961, ref. 3). The chimpanzee cardiovascular system has been extensively investigated for possible application to space research. However, a fact that we work with daily, and one which should be reemphasized, is that comparative research using the chimpanzee can be very complicated simply because of the "nature-of-the-beast." If experience has taught us anything, we know that routine complications with other nonhuman primates are usually magnified several times when using chimpanzees. Their size, strength, and destructive (inquisitive) nature would demand large, heavy, and durable flight hardware. A single animal would place great demands on a life support and waste processing system. If young animals (20 kg) could be used, some allowances would have to be made for their rapid growth during a 6-month to 1-year mission. Statistical compensations would be necessary since the number of animals that could fly would be severely limited.

At the Yerkes laboratory, only the more refined, previously explored, and proven experimental designs are applied to the chimpanzee. New techniques and approaches are first explored in a smaller, more available nonhuman primate, and when perfected, adapted to the chimpanzee. This conservative approach has proved rewarding for us and should be a consideration in selecting space flight candidates.

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# THE SQUIRREL MONKEY AS A CANDIDATE FOR SPACE FLIGHT\*

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## UNIQUE FEATURES OF SQUIRREL MONKEYS AS CANDIDATES FOR SPACE-FLIGHT EXPERIMENTS

Among the more obvious and general factors of major importance in considering the suitability of a species for space flight are size, physical and physiological characteristics (including functional capability and reactivity or sensitivity of sensory-motor systems), nutritional requirements, availability, and resistance to disease. However, while a species may be eminently suited for space travel by virtue of such biological traits or combination of traits, it is obvious that its potential value may not be fully realized if basic information at all levels of scientific inquiry is lacking or fragmentary. One of the prime requisites, then, for assessing the suitability of any species, including primates, for space flight is the availability of basic background information at all levels of scientific inquiry to insure optimal utilization of new knowledge gained through space-flight experiments. Gaps or inadequacies in such background information must invariably result in incomplete utilization of knowledge obtained from space-flight experiments, or result in serious delays in bringing the newly gained knowledge to bear on problems that have to be solved to make space flights safer for man.

For a variety of comparative and logistical reasons, the squirrel monkey has rapidly become one of the most widely used nonhuman primates in basic and biomedical research (ref. 1). Due to its small size and other unique diurnal-primate characteristics, it was the first nonhuman primate introduced into aerospace biomedical research (ref. 2). During the past 15 years, it has been used in actual space-flight missions, in an increasing number of laboratory experiments and tests conducted under unusual or flight-simulated environmental conditions, and in a wide range of descriptive or normative studies of behavior, physiology, pharmacology, and morphology. It has also been employed in research on diseases whose clarification may contribute to human health and welfare (ref. 3).

In aerospace flight research, the squirrel monkey has been utilized in at least three related roles: (i) actual bioflight missions, (ii) laboratory tests designed to clarify the risks to man during launch and recovery and in hazardous space-flight environments, and (iii) acquisition of data on unknown risks encountered in long-duration space exploration by man. In addition to the wide range of unique biological features of the squirrel monkey for aerospace flight research, the homeostatic reactions to various expected or anticipated stresses in space-flight environments can now be compared to an increasing number of normative or baseline studies of normal behavior, physiology, and morphology of this small-sized, readily available, and easily manageable higher diurnal primate (ref. 4).

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The specific aims of this review of the squirrel monkey as a space-flight candidate are to summarize the most pertinent or salient published and unpublished information available on its taxonomy, ethology, life history, sensory-learning-motor capacities in primate perspective, its distinguishing anatomical and physiological characteristics, including its homeostatic adaptation to stress, its susceptibility to environmental hazards, and its reproduction, care, clinical management, and previous use in aerospace biomedical research.

### TAXONOMIC CLASSIFICATION, NOMENCLATURE, ECOLOGY

According to the most widely used taxonomic description, the squirrel monkey, *Saimiri sciureus*, is classified as a New World plathyrrhine diurnal primate of Central and South America (ref. 5). Squirrel monkeys are found in Costa Rica, Panama, Colombia, Ecuador, Peru, Bolivia, Venezuela, Guyana, Surinam, French Guinea and Brazil (ref. 6). Although the squirrel monkey has been given many names, depending on genetic and geographic origin, at the present time, the genus and species names *Saimiri sciureus* (small squirrel-like monkey) are the most frequently used binomial designation or nomenclature (ref. 6). In one classification, the genus has been subdivided into two species and eight subspecies (ref. 7). The ecological habitat of the squirrel monkey in the tropical rain forests of Central and South America is the small branch settings in closed canopy, the shrub layers, and less frequently, the ground (ref. 7).

### ETHOLOGY

In their natural habitats, squirrel monkeys lead an arboreal life. Their locomotion is quadrupedal rather than bipedal, they seldom leap and generally climb in their arboreal life. The tail is used as an accessory locomotor and stability balancing organ (ref. 7). As in all higher diurnal primates, visually guided behavior is the most prominent behavioral characteristic of the squirrel monkey. Their hands are prehensile but the thumbs are pseudo-opposable with little evidence of selective use in manipulation, but possibly in grooming (ref. 7). The individual and social behavior of the squirrel monkey in natural habitats (ref. 8) and in seminatural environments (ref. 9) has been reported on in great detail.

### LIFE HISTORY

The maximum recorded and authenticated life span of the squirrel monkey has been reported as 21 yr. Depending upon genetic and environmental factors, median life spans have been estimated to range from 10 to 16 yr (ref. 7). The gestation period has been reported to range from 140 to 165 days (ref. 10). Female reproduction maturity has been reported as 1.5 to 3.0 yr, and male sexual maturity at 2.5 to 3.5 yr (ref. 9). With increasing knowledge on its reproductive physiology, husbandry, and clinical management, breeding in captivity has become increasingly feasible. Breeding colonies have now been established under seminatural environments at the Delta Primate Center, Louisiana, and at the Monkey Jungle in Florida.

## BODY AND ORGAN WEIGHTS OF THE SQUIRREL MONKEY

Size and weight of experimental animals represent important logistical considerations for life support systems in space-flight research. It is relevant to note that one of the more unique neurobiological features of the squirrel monkey is the very large size of the brain relative to its low body weight. In the adult male squirrel monkey, the brain is 4 percent of the total body weight (26/660 g) compared to man's 2 percent (1.4/70 kg), the chimpanzee's 0.7 percent (350 g/50 kg), the rhesus monkey's 1.5 percent (90 g/6 kg) and the tree shrew's 2.7 percent (2.7/100 g). From these allometric comparisons, the brain/body ratio of the squirrel monkey appears to be highest among all primates, including man.

For a variety of sampling reasons, there is considerable variability in the published body and organ weights of the squirrel monkey. This variability of sample means or averages is not surprising and extends to almost all types of biological data. The published sample means are generally based on a very small number of animals. Other sources of sample variability include differences in age, sex, geographic, laboratory and nonlaboratory origin, left-right laterality of some organs, nutrition and clinical condition. In order to obtain more reliable normative mean values of young adult body and organ weights as part of an ontogenetic research program, five 2-yr old Peruvian-type young adult males and five 2-yr old females of laboratory origin were sacrificed for multivariate behavioral, chemical, and morphological evaluations. Body and organ weights of these 10 monkeys were also determined and compared with published values of seven males and three females of comparable Peruvian-type, nonlaboratory origin (ref. 11). The body and organ weight sample means and their standard errors for a sample of 20 young adult squirrel monkeys are presented in table 1. Since the monkeys in the two studies combined in table 1 were of comparable age and presumably of the same geographic origin, it is apparent from the means and standard errors that sex and laterality are significant sources of differences in body and organ weights in the two samples of more carefully selected animals.

In a larger sample field study conducted at Leticia, Colombia, South America, age and sex differences in body, organ weights, physical body measurements, and such physiological variables as heart rate, blood pressure, temperature, urine pH, and leukocyte count were compared among 80 adult and 40 juvenile males and females (ref. 12). Compared to the findings presented in table 1, the above cited field study indicated that adult squirrel monkeys from Colombia, South America, are significantly heavier than those of Peru, confirming observations reported in other studies (refs. 6 and 11). Another major finding of the squirrel monkey field study was confirmation of significant age and sex differences in body, organ weights, physical measurements and several of the physiological variables.

Although many other published values on the squirrel monkey also vary considerably, it is fortunate that only the two major sources from Colombia and Peru, South America, have been developed for importation of this species to the United States. Whereas the vast majority of the increasing number of publications on the squirrel monkey do not specify the geographic origin, age, sex, or clinical status, it is frequently possible to determine the origin and taxonomic status by reference to the dealer, the physical appearance, and the average body weights of adult animals (ref. 6). It is anticipated that selective breeding of the squirrel monkey in captivity will result in significant clarification of such sources of variability as genetic and geographic origin, age, sex, nutrition, and previous history. This clarification will provide considerable improvement in the design of

longitudinal and cross-sectional sampling studies for normative data with specifications of appropriate statistical levels of confidence for the reported findings.

### MORPHOLOGICAL CHARACTERISTICS OF THE BRAIN

Due to a variety of phylogenetic and logistical reasons, the morphological features of the relatively large brain of the squirrel monkey have received considerable attention in anatomical studies. The brain of the squirrel monkey is of the "semilissencephalic" type, with a relatively smooth cortical surface illustrated in figures 1 and 2. The cytoarchitectonic and ultrastructural features of the squirrel monkey cerebral cortex (figs. 3 and 4) are very similar to those of the rhesus monkey and other primates. The overall complexity of the cortex in the rhesus monkey, as suggested by the more elaborate gyral patterns, is greater than in the squirrel monkey. Due to this relatively high level of development of the cortex in the rhesus monkey, and its popularity as an experimental subject for neurological studies, numerous investigations have been carried out on functional specificity or localization in various cortical areas. Similarly, as the advantages of the squirrel monkey as an experimental subject have come to be recognized, a number of such investigations have also been carried out in this species. Considerable information is now available on the functional characteristics of various cortical areas (refs. 13-21). Structure-function studies have provided clarification of the topographic and cytoarchitectural organization, particularly the somatosensory and visual areas of the cortex. In somatic afferent areas I and II of the cerebral cortex in the squirrel monkey, there is a relative and absolute increase in the amount of cortex concerned with the distal portions of the arms and legs as compared with lower mammals (figs. 1 and 2). The visual striate area (Brodman's area 17) in the squirrel monkey is especially well delimited by a relatively dense vasculature on the occipital pole and the laminar strip of Gennari as compared with surrounding visual areas 18 and 19 (ref. 22). The mapping of this retinal projection area on the striate cortex (fig. 5) as well as the other cortical areas noted above (figs. 1 and 2) appears to be virtually as complete for the squirrel monkey as for the rhesus monkey (ref. 23).

The interconnections of various cortical regions in the brain of the squirrel monkey have also been studied in some detail (refs. 24-27), and the efferent connections of the hippocampus were recently described (ref. 28). Other recent neuroanatomical studies in squirrel monkeys include observations on oral sensory and proprioceptive innervation (ref. 29), the thalamic projections of the nucleus caudatus (ref. 30), the organization of the inferior colliculus (ref. 31), and the distribution of crossed olivocochlear bundle terminals in the cochlea (ref. 32). In addition to the above cited studies, two stereotaxic atlases of the squirrel monkey brain have been published (refs. 33 and 34).

Recent neurophysiological investigations have also been carried out in the thalamus of the squirrel monkey (refs. 35 and 36) and in the basal ganglia (refs. 37 and 38). According to a recent review, squirrel and rhesus monkeys have been used extensively for sophisticated multivariate correlative studies of psychophysics, physiology and anatomy, particularly in sensory-learning-motor processes (ref. 39).

## SENSORY, LEARNING, AND MOTOR CAPACITY IN PRIMATE PERSPECTIVE

The most frequently cited advantages for the use of the squirrel monkey in neurobiological research are the extensive sensory, learning, and motor capacities and the very large size and weight of the brain relative to low body weight. Due in part to the unique brain/body ratio among primates, increasing interest has been directed toward the use of the squirrel monkey as a primate "model" for studying the structural and functional organization of the brain and also the effects on the brain and behavior of such environmental influences or hazards as ionizing radiation, drugs, malnutrition, various infectious diseases, and space-flight environments (refs. 2 and 40-42).

### VISION

As in all higher diurnal primates and man, visually guided behavior is one of the most prominent characteristics of the squirrel monkey. Consequently, considerable research has been devoted to examination of specific visual functions in relation to the organization of the eye, retina, and the visual pathways and centers of the brain. From behavioral studies (ref. 43), electrophysiological examinations (refs. 44 and 45) and from morphological evaluations (ref. 45), it has been established that the squirrel monkey has a relatively large eye (16 mm, 0.28 g) with a typical diurnal primate retina, including foveal cones and peripheral rods, and that the scotopic rods respond with a critical flicker fusion frequency (CFF) of 15 to 20 Hz and the photopic cones with 60 Hz to achromatic white light, as in other higher diurnal primates and man. However, the squirrel monkey is a trichromatic protonope, since it is deficient in the spectral and color discrimination and ERG-CFF responses to the longer wave lengths (red) of the visible spectrum. Major visual functions reported in the literature for the squirrel monkey based on visual discrimination testing and electrophysiological evaluations are presented in table 2.

Using a variety of behavioral discrimination methods, minimum separable binocular visual acuity thresholds ranging from 0.74 to 1.0 min of arc have been reported for the adult squirrel monkey, compared to 0.65 min of arc reported for the rhesus monkey, 0.78 min of arc for the chimpanzee, and 0.43 min of arc reported for man under similar test conditions (refs. 46-48). The binocular minimum visual acuities in minutes of arc for the squirrel and rhesus monkeys, chimpanzee and man are illustrated in figure 6.

Considerable research has also been reported on structure-function relations among photo-receptors, bipolar and ganglion cells in the retina of the adult squirrel monkey (ref. 45), and also on the topographic or point-to-point projection or representation of the fovea and macula on the lateral geniculate bodies (LGB) and the striate cortex in relation to visual acuity and spectral sensitivity (refs. 22 and 23). Receptive fields of color (ref. 49) and for single unit responses involved in the columnar and horizontal organization of the striate cortex have also been established for the squirrel and rhesus monkeys (ref. 50). The topography of the retina and striate cortex and its relationship to visual acuity have also been compared between the squirrel and rhesus monkeys (ref. 18).

## AUDITORY THRESHOLDS

Although experimental studies are few in number, it is apparent that the squirrel monkey auditory system is highly developed, since it utilizes sounds as sources of information in its environment, including in its communication within a highly complex social organization (refs. 40 and 51). According to two published behavioral studies, auditory threshold curves of the squirrel monkey appear to be of the same shape as reported for other primates and man. Figure 7 illustrates a threshold of hearing curve for a sample of three adult squirrel monkeys reported in behavioral studies (refs. 40 and 52). In another behavioral study, audiograms of two adult squirrel monkeys were compared with those of the rhesus and cynomolgus monkeys. Audiograms were inferred from auditory discrimination elicited under shock and reward test conditions (ref. 53). Since the determination of such auditory functions as pitch and loudness in audiograms in relation to sound intensity and frequency is highly complex and subject to many complex methodological problems, it should be recognized that the auditory threshold curve based on a sample of three subjects and presented in figure 7 should be interpreted only as a tentative normative hearing curve for the squirrel monkey.

## VESTIBULAR FUNCTIONS

Recent studies have indicated that, in close association with the visual system, the vestibular system of the squirrel monkey provides information on the position of the head and neck in spatial orientation and that it is also intimately involved in reflex postural adjustments and the maintenance of bodily equilibrium in response to gravitational forces (ref. 54). Due in part to increasing interest on the effects of gravity and weightlessness on man and nonhuman primates in space flight environments, considerable research has been reported on the squirrel monkey as an ideal experimental model in visuo-vestibular research. In a series of experiments extending over the past 10 yr, the usefulness of the squirrel monkey has been demonstrated for studies of spatial orientation, positional and optokinetic nystagmus, and changes in bodily equilibrium after vestibular end-organ, cervical, and cerebellar lesions or ablations, visual cue alterations, and antibiotic ototoxicity (ref. 55). Other studies have examined behavioral responses of unrestrained normal and labyrinthectomized squirrel monkeys to repeated zero-gravity parabolic flights (ref. 56). Squirrel monkeys have also been trained in a centrifuge to escape and avoid changes in artificially induced gravity (ref. 57). Total darkness (ref. 58) and centrifugally-produced gravity (ref. 59) have also been studied as aversive stimuli for the squirrel monkey.

The squirrel monkey has been shown to be susceptible to canal sickness induced by a slowly rotating room (ref. 60). Counterclockwise rotation at rates between 1.9 and 2.6 rpm, with the animals in a cage 4 ft from the center of the axis of rotation, was effective in inducing emesis with a latency of less than 10 min (table 3). Prior to emetic testing, the animals were evaluated for sensitivity of the vestibular system to reduced temperatures determined by cold water caloric nystagmus tests (table 3). The threshold responses occurred at water temperatures of from 24° to 30° C.

At 7 months following unilateral left labyrinthectomy in three animals, nystagmus could not be elicited through left caloric testing, and the threshold to right caloric testing was elevated to between 32° and 33° C. However, vomiting was elicited in all of the animals at rotational speeds

from 2.6 to 3.8 rpm. Following bilateral labyrinthectomy in three animals, there was no response to caloric testing in either ear 7 months following the surgery. All three animals exhibited a permanent disturbance of equilibrium, and none exhibited the emetic response or any of the prodromal signs of canal sickness. In another study, five Colombian squirrel monkeys were found to be "motion sickness sensitive" while the remaining six, of a group of 11, were not (ref. 61). The results are summarized in table 3. The motion sickness tests were carried out as described above. The animals were rotated at 10 rpm until emesis occurred or until 15 min had elapsed. Caloric tests carried out in these animals revealed no significant differences in threshold values for the right and left ears. The experiments also showed that a normal threshold caloric response was not necessarily indicative of motion sickness susceptibility, nor was the reverse true. However, positive emetic responses were predictive of normal end-organ morphology, threshold caloric test value, and semicircular canal function in at least one ear. A lack of emesis in the rotation test had no predictive value and provided little information for screening purposes. No significant pathology was observed in these animals in either the middle or inner ear, nor has there been observed overt evidence of labyrinthine disease (e.g., aural discharge or equilibratory problems) in a large number of squirrel monkeys in the colony of the Delta Primate Center. From the above reports and observations at the Delta Primate Center, it appears reasonable to conclude that inner ear pathology is rare in well-screened animals and should not constitute a serious problem from the standpoint of suitability of the squirrel monkey for space-flight research.

The experiments on canal sickness and emetic threshold to rotary motion cited above have demonstrated that the manifestations of canal sickness in the squirrel monkey almost certainly have their genesis in the semicircular canals. However, little information is available on structures mediating the emetic response to canal sickness below the level of the labyrinths.

In preliminary studies directed at the latter problem at the Delta Primate Center and the NASA Ames Research Center, it has been observed that the incidence of canal sickness to rotary motion at 50 rpm, as evidenced by emesis, was 48.8% in single tests on 29 animals. The latency of the response in the sensitive monkeys varied from 12 to 90 min, averaging 45 min. The animals in these experiments were placed in a lucite restraining chamber at the center of the axis of rotation. The restraining chamber maintained the animals in a standing position, but allowed free movement of the head and neck. Bilateral ablation of area postrema in three of the motion-sickness susceptible squirrel monkeys eliminated the emetic response to rotary motion. The same animals also failed to respond to the intramuscular injection of 50 mg/kg of 5-hydroxytryptophane, a powerful emetic stimulant which had elicited a strong emetic response in preoperative tests. These preliminary experiments suggest that the organization of the central emetic apparatus in squirrel monkeys is very similar to that in other mammals including nonhuman primates (refs. 62-65) and man (ref. 66).

## CHEMICAL SENSES

It is generally accepted that there is an interaction of sensory information from the chemical senses of smell and taste. Even in microsmatic species, including primates, qualitative aspects of taste are attributable to stimulation of the olfactory system since taste responses include only sour, sweet, bitter, and salt. Although considerable information has been obtained in psychophysical tests and correlated single unit neural responses of chemical receptors, only two studies of taste and none on olfaction in the squirrel monkey have been reported. In a genetic chemoreception study of taste polymorphism in the squirrel monkey using phenol-thio-carbamide, 95 percent of a sample of 14



were observed to be "tasters" (ref. 67). Using paired comparison methods, glucose preferences were discriminated by four squirrel monkeys among 5 percent, 10 percent, 20 percent, 30 percent, and 40 percent glucose solutions after 10 and 60 min (ref. 68). Recent studies of olfaction in marmosets suggest the possible use of pheromones for scent marking of territory, sex identity, and communication among New World platyrrhines, including the squirrel monkey (ref. 69). Table 4 summarizes available information on taste and possible role of olfaction in the squirrel monkey.

## DELAYED RESPONSES

Delayed response tests have been proposed as one of the most sensitive behavioral tests for phylogenetic differentiation of spatial orientation, learning, and retention of symbolic cue utilization (ref. 70). Squirrel monkeys have been exposed to visual cues located in relation to incentives, and after various enforced periods of delay, they have been permitted to obtain the incentive. Among primates, the squirrel monkey has been classified between marmosets and rhesus monkeys on delayed response tests (ref. 71). In broader comparative perspective, cats and raccoons show almost no retention of cues after 30 sec, marmosets and gibbons show 70 percent to 75 percent, the squirrel monkey 70 percent and the rhesus monkey responds by 80 percent retention after 30 sec delays (ref. 70). Figure 8 illustrates the delayed response performance of the squirrel monkey in relation to other primates.

## LEARNING-SET

There has been an increasing use of Learning-Set as an estimate of basic intelligence among primates, including man. It has been suggested that Learning-Set capacity in phylogenetic rank is closely related to evolutionary position and probably to cortical complexity. The Learning-Set performance of the squirrel monkey in phylogenetic rank has been reviewed extensively (ref. 40). According to several studies, the squirrel monkey appears to be inferior to the rhesus monkey, the apes, and man, but superior to the marmoset, cat, raccoon, and rat (refs. 72-74). The squirrel monkey has also been used extensively in the assessment of discrimination-reversal performance in phylogenetic perspective (ref. 40). From a review of the extensive literature on the learning capacity of the squirrel monkey in primate perspective, it seems reasonable to conclude that it is at least in the middle range of the primate order, ranging from the controversial taxonomic status of the tree shrew to man. Figure 9 illustrates the status of the squirrel monkey in the primate rank-order Learning-Set hierarchy.

## PERFORMANCE CAPACITIES

As in all higher diurnal primates, the perceptual-motor skills of the squirrel monkey are closely related to increasing encephalization and precise localization of sensory-associative-motor regions in the brain, particularly in the cerebral cortex. Eye-hand coordination is highly developed, although the thumb appears pseudo-opposable in manual dexterity and manipulation of objects. Compared to the rhesus monkey, the squirrel monkey's manipulatory skills of objects, particularly home cage locks and other security devices are quite inferior. However, with some modifications in procedures and test devices, the squirrel monkey has demonstrated adequate motor skills in the following sensory-learning motor performance tests in unrestrained and restrained conditions: (i) Wisconsin

General Test Apparatus (WGTA), (ii) operant condition (bar pressing and string pulling devices), (iii) runways, (iv) mazes, (v) patterned string problems, and (vi) rail and (vii) platform tests of equilibrium. A summary of the motor performance tests used with the squirrel monkey under unrestrained and restrained test conditions is presented in table 5.

## PHYSIOLOGICAL CHARACTERISTICS

### CARDIOVASCULAR SYSTEM

#### Blood-Cell Morphology, Hematology

Capel-Edwards and Hall (ref. 75) carried out a comprehensive study of the blood-cell morphology of squirrel monkeys in 31 females and 3 males.

#### Blood-Cell Morphology

*Red cells.*— There was a mild to moderate anisocytosis in all films. Anisochromasia was present in most films but frank hypochromasia was also present.

*Neutrophils.*— These were similar to human neutrophils in size and general appearance, often with pronounced spherical azurophilic cytoplasmic granulation, unlike the neutrophils of other laboratory animals such as the rat and dog. However, vacuolation and changes associated with toxic states were not seen, even in "obviously sick" animals. The number of nuclear segments varied from four to six. Juvenile neutrophils or metamyelocytes were rarely seen, and earlier myeloid cells were absent.

*Eosinophils.*— These were large cells with the cytoplasm packed with very small round orange-yellow or brick-red granules not extending beyond the margins of the cell as is seen in some laboratory animals, including the horse. The nucleus was always clearly visible but nuclear segmentation was variable. Metamyelocyte and juvenile forms were often seen.

*Basophils.*— These cells were almost identical to those in man in size and staining characteristics but very few in number.

*Lymphocytes.*— Four distinct types of lymphocytes were observed. In the first type the cells were about 7  $\mu\text{m}$  in diameter with a round or bean-shaped densely stained nucleus and a thin rim of deep blue cytoplasm. These were very few in number. In the second type, the cells were very similar to human lymphocytes, from 8 to 12  $\mu\text{m}$  in diameter, with a round, oval or slightly irregular nucleus. A third type resembled the "granular fever" cell of man. The nucleus was highly pleomorphic with coarse strands of chromatin, and light to moderate basophilia. A fourth type had very pale, sometimes foamy, blue cytoplasm containing a bilobed nucleus.

*Monocytes.*— These were 15 to 20  $\mu\text{m}$  in diameter, with irregular pale, smooth staining nuclei, and a cloudy blue cytoplasm.

*Plasma cells.*— These types of cells were not observed.

Baseline and normative hematological and serum chemistry values of adult male and female squirrel monkeys have been estimated from four published and one unpublished studies (refs. 11 and 75-77; unpublished values from the Delta Primate Center).

### Hematology

Data on packed cell volume, hemoglobin, etc., are given in table 6, while values for blood chemistry are listed in table 7. It will be observed that many values are closely comparable to those in man.

The blood platelet count in squirrel monkeys was reported by Capel-Edwards and Hall (ref. 75) as  $448 \pm 64$  (mean,  $\pm$ S.E.). The sedimentation rate at 1 hr varied between 0.5 and 4.0 mm and at 2 hr between 1.0 and 16 mm in nine normal female subjects. Coagulation data in 10 adult females under Sernylan sedation were as follows: Quick's one-stage prothrombin time (rabbit brain)  $7.7 \text{ sec} \pm 0.6$ ; Russell's viper venom time  $11.3 \text{ sec} \pm 0.4$ ; Kaolin cephalin time  $26.0 \text{ sec} \pm 1.1$ ; thrombin time with 50 N.I.H. units  $10.8 \text{ sec} \pm 2.1$  and with 5 N.I.H. units of  $23.1 \text{ sec} \pm 3.5$ . The thrombotest gave a mean value of  $18.5 \text{ sec} \pm 1.1$ .

### Cardiac Function

*Heart rate.*— According to Middleton and Rosal (ref. 12) the heart rate was  $235 \pm 12$  in fully adult males ( $n=12$  ( $n=\text{sample}$ )),  $251 \pm 14$  in juvenile males ( $n=17$ ), and  $241 \pm 11$  in juvenile females ( $n=22$ ). Kupper and Britz (ref. 4) noted that the heart rate in adult monkeys varied from 250 to 300 beats/min.

*Blood pressure.*— The systolic pressure was  $132 \pm 5$  mm Hg in adult males ( $n=12$ ),  $139 \pm 6$  mm Hg in juvenile males ( $n=17$ ), and  $146 \pm 5$  mm Hg in juvenile females ( $n=22$ ). Diastolic pressure in the same groups were  $80 \pm 3$ ,  $97 \pm 4$ , and  $102 \pm 4$ , and the pulse pressures were  $52 \pm 3$ ,  $42 \pm 2$ , and  $45 \pm 2$  mm Hg, respectively (ref. 12). In studies on 12 adult male squirrel monkeys with indwelling plastic aortic cannulas, a mean aortic pressure of 130 mm Hg was observed with pressure pulses between 50 and 55 mm Hg (ref. 78). In a study of behavioral effects on blood pressure, a mean value of  $135 \pm 1.84$  mm Hg was reported in five control adult male squirrel monkeys (ref. 79).

*Behaviorally induced hypertension.*— Five adult male squirrel monkeys (775 to 990 g) were subjected to chair restraint and periodic electrical stimuli (650 Vac, 60 Hz, 2 to 10 mA for 200 msec) and trained to ward off the stimuli by pressing a key (ref. 79). The mean blood pressure was  $167.5 \pm 2.48$  mm Hg during experiments in unanesthetized monkeys,  $174.7 \pm 3.52$  when placed in an isolation chamber after the experiments and  $144.5 \pm 2.50$  mm Hg when returned to their cages following the conclusion of the experiments. Arterioles from the renal cortex of the stressed animals showed narrowing of the lumen and thickening of the wall due to deposition of amorphous substance, mainly in the media. The results were interpreted to signify that operant conditioning schedules, which continuously exert strong control over an animal's behavior, also induce marked, persistent elevations in mean systemic arterial pressure.

### *Electrocardiogram. —*

a. Normal pattern and common variants: The great majority of electrocardiograms (ECG) in 140 males and 128 female Brazilian squirrel monkeys resembled those in man (fig. 10). This was notwithstanding the faster rate. They were also similar to those for other nonhuman primates (refs. 80 and 81). Sodium thiopental anesthesia did not alter the electrocardiogram. In 23 percent of the animals tall, spiked P-waves were seen in leads II, III, and AVF. The significance was not known, but this pattern has been associated with increased vagal tone and respiratory sinus arrhythmias in dogs and right atrial enlargement in man.

One animal of the group had electrocardiographic changes compatible with left ventricular hypertrophy. Following the death of this animal, a markedly enlarged heart (7.35 g; normal  $3.3 \pm 0.11$  g) with a thickened left ventricle was found. Marked variation in T-wave form was seen in all leads. In 15 animals, isoelectric or inverted T-waves were seen in leads I, II, or III, and believed to be associated with cardiac diseases. However, neither P-wave variation nor supraventricular tachycardia have been seen in the squirrel monkey.

### b. Effects of calcium and potassium:

(1) Hypercalcemia: The electrocardiogram of the hypercalcemic squirrel monkey resembled that of man with an actual shortening of the QT interval (fig. 11). The ST segment was markedly shortened or absent and the T-wave appeared directly after the ventricular depolarization complex. The QT duration was correspondingly decreased. Arrhythmias or conduction delays were not seen with serum calcium levels of 15 to 19 mg percent. It was believed that the toxic level of serum calcium may be higher for the squirrel monkey than for man or dog. A concurrent increase in serum phosphorus was considered negligible.

(2) Hypocalcemia: In this condition there was a markedly prolonged ST segment, and decreased amplitude of T-waves (fig. 12). Four of five animals developed a marked bradycardia (160 to 200/min). Serum potassium levels were within the normal range.

(3) Hyperkalemia: There was a widening and lowering of the QRS complex and elevation and "tenting" of the T-wave (fig. 13).

The above study supported the view that the principles used in the interpretation of the ECG's in man are applicable to the interpretation in the monkey.

c. Effects of stress: During stress induced by restraint for 100 hr or more and training in Sidman avoidance of electrical tail shock (1 sec; 4 mA) ( $n=8$ ), an initial tachycardia (20 percent  $<$ ) was observed in all monkeys followed after the first hr by bradycardia (ref. 82). ST-segment elevation and T-wave changes were seen in four of the animals and QRS lengthening, deep symmetrical T-wave inversion, and a descending ventricular pacemaker were seen prior to cardiac arrest in another animal.

On microscopic examination, lesions were observed in the myocardium of all stressed animals. This was characterized by fuchsinophilia and fibrosis, with a full spectrum of myocardial tissue repair ranging from necrosis, cellular infiltration, and fibroblastic proliferation to acellular collagen formation. Comparison of the lesion data with stress and ECG indicated no relationship between length of exposure to avoidance procedure and the ECG. Furthermore, separation of all monkeys on the basis of the ECG rating, and comparison with lesion ratings showed no correlation between the extent of

myocardial damage and the degree of ECG disturbance. The severe bradycardia suggested that parasympathetic activity played a dominant role in the ECG changes observed.

### Role of Autonomic System in Control of Heart Rate

In a study by Life and Pince (ref. 83), on the role of the sympathetic and parasympathetic nervous system in accelerative bradycardia, 29 squirrel monkeys were exposed to  $200 + G_x$  for 200 sec on an articulated centrifuge. Following centrifugation, the heart rate of all animals decreased below baseline values during the initial 25 to 50 sec of exposures. However, animals which were atropinized maintained the highest rates, those treated with hexamethonium showed somewhat lower rates, and control animals exhibited the most profound bradycardia. The authors interpreted the results as indicating an augmentation of an intrinsic bradycardia response by a predominant parasympathetic influence. The cardiac rate inhibition was opposed by sympathetic influence, but the latter was much weaker than the parasympathetic effects.

## RESPIRATORY SYSTEM

### Respiratory Rate

The respiratory rate in healthy squirrel monkeys varied from 40 to 60 excursions/min (ref. 4). In animals restrained in a light-tight chamber for a 24-hr period, the respiratory rate was fairly stable at about 60/min after an initial moderate elevation (ref. 11). Aside from these values, however, there is virtually no information on respiratory functions in the squirrel monkey.

## DIGESTIVE SYSTEM

Although considerable data are available on nutritional requirements and metabolic characteristics in the squirrel monkey there is very little information on the morphological or physiological characteristics of the digestive system in this species.

## NUTRITION

Although squirrel monkeys have been used extensively and with increasing frequency in biomedical research, until recently, relatively little scientific information was available concerning their nutritional requirements. Recently, more careful observations have been made on their feeding habits in their natural habitat, including examination of intestinal contents. Numerous studies have also been reported on the nutritional requirements of the squirrel monkey under normal laboratory conditions and on the use of solid food pellets and various liquid diets for reinforcement in basic and nutritional research. In their natural environment, squirrel monkeys have been reported to eat fruits, nuts, buds, and a variety of insects, as verified by examination of intestinal contents (ref. 8). According to more extensive studies of the nutritional requirements of the squirrel monkey in

captivity, it requires a diet of high caloric density (ref. 84). A semipurified diet has been developed and used extensively for several years in nutritional studies of New World primates. The only unusual feature concerning the diet for the squirrel monkey is the specific requirement for vitamin D<sub>3</sub> (ref. 82). Other studies have suggested that squirrel monkeys require an exogenous source of vitamin C (ref. 85). In several studies, complete diets in tablet and liquid form have been used successfully over short periods as reinforcement and sole sources of the nutritional requirements during behavioral-discrimination testing (refs. 86 and 87). The nutritional and dietary requirements of the squirrel monkey in its natural habitat, laboratory, and in pellet and liquid form for research are presented in table 8.

## METABOLISM

### Carbohydrate Metabolism

Squirrel monkeys are among the few species of nonhuman primates in which clear-cut abnormalities in carbohydrate metabolism have been demonstrated. Davidson *et al.* (ref. 88) showed that 16 of 30 female Colombian animals given a standard glucose tolerance test, as modified for squirrel monkeys, (4 g dextrose/kg body weight) gave abnormal responses, while the remaining 14 were normal (table 9). In the "normal" group, the blood glucose, in diagnostic tolbutamide tests, decreased to 50 percent of the fasting levels within 30 min, then slowly increased to about 65 percent of normal. The abnormal responses, on the other hand, were characterized by a much slower gradual decrease in blood glucose from fasting levels. A response to the diagnostic tolbutamide was considered abnormal if the percentage of the initial fasting blood sugar was greater than 75 percent at 20 min.

Glucose tolerance tests carried out in 200 normal adult Colombian squirrel monkeys (ref. 89) revealed that adult animals had significantly higher (52.59 percent abnormal;  $n=35$ ;  $p < 0.001$ ) glucose tolerance test values than juveniles (27.69 percent abnormal;  $n=65$ ;  $p < 0.001$ ). It was further shown that adult males ( $n=106$ ) exhibited higher (57.55 percent abnormal) glucose tolerance test values than adult females (34.48 percent abnormal;  $n=29$ ;  $p = 0.02 < 0.05$ ) but there was no significant sex difference in juvenile animals (table 9). These patterns of response were generally similar to human responses to the same tests and there was no change in the response over a period of 9 weeks during which several such tests were carried out. In further experiments, a group of 10 monkeys (5 normally responding and 5 nonresponding to diagnostic tolbutamide tests) was treated daily with oral tolbutamide (15 mg/kg b.i.d.) over a period of 6 weeks. They were tested for their response to diagnostic intravenous tolbutamide after 2 and 6 weeks of treatment. The response of three of the "abnormal responders" was unchanged, but two such animals appeared to benefit from the treatment. After 6 weeks of tolbutamide treatment a diagnostic tolbutamide test revealed that three of five original "nonresponding" monkeys were sufficiently improved to give a normal response.

In the experiments described above, the proportion of abnormal responders exceeded the expected human incidence, but none of these animals demonstrated overt signs or symptoms of diabetes. However, animals with overt diabetes mellitus were found within the colony. These few incidences were found when apparently healthy monkeys entered into a phase of rapid physical deterioration with loss of weight followed by death, all occurring within a few days. Two of these

animals with blood glucose levels of 510 and 750 mg percent, respectively, glycosuria, and polyuria exhibited marked degranulation of the pancreatic islets and showed fatty streaks and plaques in the aorta at autopsy.

Lang (ref. 89) has suggested that the "improvement" of carbohydrate metabolism demonstrated in the above described experiments might actually have a genetic basis. He noted that insulin affects both the synthesis of fatty acids in, and the release of fatty acids from, adipose tissue. According to this view, "impaired" animals would be more likely to accumulate depot fat when food is plentiful which would help them to survive the dry season, whereas the "normal" animal without these reserves would be more susceptible to dehydration, protein depletion, and subsequent death. The possible implications of this hypothesis for space flight are not known at the present time. However, in relation to the qualifications of animals for space flight, it is the opinion of the present authors that the screening procedures should include diagnostic tolbutamide tests and cortisol glucose tolerance tests. Results of these tests would permit selection of animals with maximal predictability and stability with reference to their suitability for space flight from the standpoint of carbohydrate metabolism.

### Protein

The effects of a semisynthetic diet with four different protein levels have been examined in the squirrel monkey. Twelve young male squirrel monkeys were assigned for 24 weeks to four isocaloric diets with 25 percent, 12.5 percent, 9 percent, or 6 percent protein. The protein diet consisted of purified soya protein, but it was supplemented with 2.1 g percent methionine to maintain the same content of this amino acid normally present in casein. The effects of 25 percent and 12.5 percent protein did not differ significantly on many variables examined; however, the 9 percent and 6 percent protein diets resulted in poor ponderal growth; decreased albumin/globulin ratio, hemoglobin, and BUN; but increased serum alkaline phosphatase. The livers of the 2 low-protein groups had moderate to severe ultrastructural changes (ref. 90).

### Lipid Metabolism

**Cholesterol.**— The squirrel monkey shares with man a limited ability to absorb cholesterol from the diet (ref. 91). For this reason, massive cholesterolemia does not occur in this species as it does in rhesus monkeys on diets with a high cholesterol content. In an investigation of cholesterol feeding, together with various fats and oils, for a 2-yr period, Lofland *et al.* (ref. 92) observed that plasma cholesterol levels were lower in animals fed cholesterol and safflower oil than in those fed cholesterol and butter. In the whole carcass, the amount of cholesterol was the same in the two groups, but the studies did indicate that the blood level was greatly influenced by the degree of saturation of the fat in the diet. Coronary atherosclerosis was demonstrated by Maruffo and Portman (ref. 93) in squirrel monkeys fed on cholesterol diets. After 3 months on such diets, coronary artery lesions of a proliferative and degenerative nature were seen. The cardiac tissue in these animals also revealed calcification, fragmentation of elastic laminae, proliferation of collagen and the presence of stainable mucopolysaccharides. These lesions resembled those seen in human subjects much more closely than those produced in any previous experimental studies.

**Lecithin.**— In the same study, increases in the lecithin content of the aortic intima and inner media were observed in animals with atherosclerosis induced by dietary regimens.

## Temperature Regulation

The relation between behavior and physiology in the thermoregulatory response of the squirrel monkey has been extensively studied by Stitt and his colleagues (refs. 94 and 95) in squirrel monkeys unilaterally implanted with thermode and thermocouple reentrant tubes in both the medial preoptic area of the hypothalamus and the rostral portion of the midbrain reticular formation. These workers were not able to show that a direct thermal stimulation of the midbrain alters either metabolic rate or behavioral thermoregulatory responses (voluntary choice between two preset aversive air temperatures, 10° and 50° C) while direct stimulation of certain sites in the hypothalamus and preoptic region did modify such responses. They have postulated that, in the intact animal, the midbrain has no direct sensory function in thermoregulation, but, in the event of injury to such major control centers as the hypothalamus, the midbrain could be brought into play to exert at least rudimentary control over thermoregulatory responses. The effects of the two tranquilizers chlorpromazine and haloperidol have been examined on rectal temperature in the squirrel monkey over a period of 4 weeks with daily injections of the two drugs (Ordy *et al.*, unpublished observations). Chlorpromazine and haloperidol significantly reduced rectal temperature throughout the 4-week period. Figure 14 illustrates the effects of CPZ and HPD on rectal temperature in the squirrel monkey.

## Oxygen Uptake

The oxygen uptake of fasting squirrel monkeys has been found to be slightly over 800 mliter O<sub>2</sub>/kg/hr, which approximates a daily intake of about 95 cal/kg/day. Values (cal/kg/day) for other nonhuman primates are given as 29.2 for the chimpanzee, 48 for the baboon, and 48 to 49 for the rhesus monkey. However, when heat production is calculated on the basis of cal/kg<sup>3/4</sup>/day, homothermic mammals including man produce 70 cal/kg<sup>3/4</sup>/day. With this same calculation, the squirrel monkey is comparable, though still higher, at 91 cal/kg<sup>3/4</sup>/day (ref. 96).

## EXCRETORY SYSTEM

### Renal Function

Urine volume (mliter/24 hr) in squirrel monkeys (ref. 97) has been reported as 9.0 to 20 in male (420 to 860 g, two determinations) and 9.5 to 23 in females (580 g, two determinations). In another report, the 24-hr volume is given as 8 to 15 mliter (ref. 98).

Values of various components of renal function in adult animals as reported by Tanner and Selkurt (ref. 99) are given in table 10. After hemorrhage and transfusion, the glomerular filtration rate was reduced, a larger than normal fraction of filtered water was excreted, and the urine was essentially isoosmotic to plasma. Fractional reabsorption of water in surface proximal tubules was normal. Distal fluid osmolality, which was always hypoosmotic to plasma before shock, was sometimes isoosmotic after shock. Kidney papilla osmolality was markedly reduced after shock. The loss of urinary concentrating ability was considered to be due to washout of the medullary gradient during hypotension. Hemorrhagic shock did not produce significant tubule damage.



From studies on renal concentrating mechanisms, involving infusion of hypertonic mannitol and ADH, Selkurt and Wathen (ref. 100) concluded that the kidney of the monkey appeared to operate like the human kidney, in contrast to that of the dog, which manifests incomplete osmotic equilibration in the distal tubule and collecting duct. With sustained mannitol diuresis, it has been observed that the  $T^C H_2 O$  decreased in man as in the monkey. The rat kidney stands at the other extreme in which, as osmolar excretion increases during progressive mannitol diuresis, the  $T^C H_2 O$  also rises progressively.

### Fecal Excretion

In preparation for a long-duration orbital flight, the excretion of two squirrel monkeys was determined under various environmental and dietary conditions. A daily excretion of 15 g was observed under normal solid food conditions. The daily excretion was reduced to 3 g with a low-residue liquid diet (ref. 2).

## NEUROENDOCRINE AND AUTONOMIC SYSTEM, STRESS

### PITUITARY AND ADRENAL HORMONES

In a series of neuroendocrinological studies of the squirrel monkey, hypothalamus-pituitary-adrenal responses have been examined under so-called "baseline" conditions, as well as in response to handling, restraint, and other test conditions (refs. 101-103). Hypothalamic lesions were produced in the squirrel monkey to identify nuclei and pathways involved in the control of stress-induced changes in growth hormone (GH) and cortisol, the major adrenal and plasma corticoid in this species (ref. 102). Plasma levels of cortisol in resting, undisturbed caged animals were uniquely high at 405  $\mu$ g percent  $\pm$ 43 (ref. 101). However, the bound fraction of plasma cortisol was not greater than in other primates. Adrenal cortical function was inhibited only by relatively large doses of dexamethosone and was relatively unresponsive to exogenous ACTH.

### RESPONSE TO PSYCHOLOGICAL STRESS

The squirrel monkey has been used with increasing frequency in studies of stress with particular emphasis on the effects of neuropharmacological agents acting on the nervous system and on the neuroendocrine organs (ref. 42). Growth hormone and cortisol levels were higher during the excitement of stress of capture (10.8 mg/mliter) than in resting animals (3.9 mg/mliter). The corresponding values for plasma cortisol in the same situations were 755.7  $\mu$ g percent and 404.9  $\mu$ g percent, respectively (ref. 103). Capture appeared to be the most consistently stressful stimulus observed in these studies. During chair restraint, a dissociation of hormone response occurred. Growth hormone remained at resting levels (5.3  $\mu$ g/mliter), but cortisol rose to a plateau level of 1090.6  $\mu$ g percent in from 60 to 90 min. The turnover rate of cortisol was very high (30 mg/day). When subjected to an intense sound stimulus, one of five chair-restrained animals showed a moderate increase in growth hormone levels, but no change in cortisol values. The other four animals exhibited no significant changes. During training, relative to studies involving aversive conditioning to electric shock, the animals showed an elevation in growth hormone, but no change in cortisol

levels. Later there was no change in levels of either hormone in animals which successfully avoided the electric shock stimulus.

## EFFECTS OF STRESS, TRANQUILIZERS, AND ANESTHETICS ON HYPOTHALAMIC, CAUDATE, AND CARDIAC CATECHOLAMINE LEVELS

Concurrent changes in hypothalamic and cardiac catecholamines were examined in the squirrel monkey after stress produced by social isolation and electric shock, and after administration of anesthetics and tranquilizers (ref. 104). Social isolation and electric shock and the administration of anesthetics depleted hypothalamic and cardiac norepinephrine concentrations. Pretreatment of chlorpromazine and haloperidol effectively inhibited electric-shock-induced depletion of hypothalamic and cardiac catecholamine concentrations. In another study, significant increases were observed in pituitary ACTH concentration of the squirrel monkey after 30 days of exposure to 1-hr daily electric shock. The tranquilizers chlorpromazine and haloperidol also inhibited the stress-induced increases in pituitary ACTH concentrations (Ordy *et al.*, unpublished observations). Haloperidol and electric interaction effects on tremors and on catecholamine concentrations in the caudate nucleus of the squirrel monkey have also been reported (ref. 105).

## ADRENAL MEDULLARY HORMONES

Biochemical, histochemical, ultrastructural observations have indicated that the chromaffin cells of the squirrel monkey adrenal medulla contain only epinephrine, rather than a combination of epinephrine and norepinephrine, generally characteristic of higher diurnal primates and man (ref. 106).

## CIRCADIAN RHYTHMS

Recent studies have shown an increasing interest in circadian oscillations and their effects on the organization of organs, including the nervous system. Circadian oscillations may provide a framework for the temporal organization of all biological activity ranging from single cells, tissues, organs, and the behavior of the organism. Changes in biorhythms have been studied in response to light and temperature cycles, in animal navigation, sleep-wake cycles, and in a host of other biological functions synchronized or entrained by environmental forces. In response to the increasing recognition of biorhythms in biology and the effect of space-flight environments on "biological clocks," a symposium was organized on circadian rhythms in nonhuman primates as part of the Second International Congress of Primatology (ref. 107). The published proceedings of that symposium contain papers on both behavior and physiological biorhythms in the chimpanzee, baboon, rhesus, and capuchin monkeys. Major topics included biorhythms and behavior, the central nervous system, and the effects on the cardiovascular system and on metabolism. Although it was concluded that there may be considerable generality in Simian biorhythms, no specific reference was made to the squirrel monkey.

## SUSCEPTIBILITY TO ENVIRONMENTAL HAZARDS

### EFFECTS OF IONIZING RADIATION

In 36 female adult squirrel monkeys exposed to 800-R whole-body X-irradiation, diarrhea, vomiting, and conjunctivitis were noted during the first 24 hr (ref. 108). Later, the animals became anorectic and listless, and petechiae were observed over much of the body surface. Anemia, leukopenia and thrombocytopenia became progressively more severe. Terminal bacteremia occurred in most animals just before death. Gross examination revealed extensive hemorrhage, edema, focal tissue necrosis, and numerous bacterial foci throughout the body. The bone marrow was hypocellular, as were the lymph nodes and spleens. The dose in the above study was sufficiently high that the observed physiological and pathological changes are not surprising and might be expected to occur in virtually any mammalian species under the same conditions of exposure. From the descriptions of these authors, it does not appear that any unusual radiation sensitivity was evident in the squirrel monkeys.

### EFFECTS OF LOW-FREQUENCY MAGNETIC FIELDS

Studies on behavioral effects of exposure to extremely low frequency magnetic fields have been carried out recently by Grisset and deLorge (ref. 109) and Grisset (ref. 110). The behavioral test consisted of requiring the animals to press a lever, within a 3 sec interval indicated by a light stimulus, to receive the reinforcement of a food pellet. Three indices of performance were computed from the behavioral data: (i) reinforcement ratio — the average number of correct responses required to receive one pellet; (ii) efficiency ratio — the ratio of correct responses to the total number of responses for one session; (iii) reaction time — the interval between the onset of the light stimulus and release of the lever for all correct responses. In one series of experiments three animals were exposed for 1 hr daily to a 3-G magnetic field at 45 Hz, and another series was carried out at 7 Hz. In another study (ref. 110) the same animals were later exposed continuously for 42 days to a 10-G magnetic field at 45 Hz.

No significant differences were observed between control and experimental animals in either the short-exposure or long-exposure experiments. The authors concluded that central-nervous-system (CNS) performance in the squirrel monkey, as measured by the particular behavioral parameters employed, was insensitive to the specific magnetic-field conditions used.

### INFECTIOUS, PARASITIC, AND DENTAL DISEASE

Disease conditions to which squirrel monkeys are susceptible (ref. 4) are outlined in table 11. In regard to tuberculosis, Kupper and Britz (ref. 4) recommended adequate quarantine and routine tuberculin testing in squirrel monkey colonies, but called attention to the peculiar sensitivity of squirrel monkeys to tuberculin.

Salmonella organisms have been repeatedly isolated from squirrel monkeys, but a definite association with disease in this species has not been established (ref. 111). The most extensive lesions

from *Actinobacillus* have been seen in the kidney (ref. 112), where large bacterial emboli, cortical necrosis, hemorrhage, and glomerular microabscesses were found.

Lesions from yellow fever virus of the arbovirus group (ref. 113) included typical midzonal hepatic necrosis with Councilman body formation. Animals from yellow fever areas obviously require close observation and attention to quarantine protocols. Serologic evidence of dengue virus (ref. 114) and Melao virus (ref. 115) has been reported, but clinical illness has not been established for these organisms.

*Herpes tamarines* is generally carried as a latent infection and clinical disease has been reported (ref. 116). The animals exhibit scab-covered lesions of the lips and necrotic plaques on the mucous membranes of the tongue and hard palate. The disease is self-limiting in squirrel monkeys but infected squirrel monkeys should not be housed with other New World primates.

Rabies has been reported in three squirrel monkeys (ref. 117) and serologic evidence to reovirus has been reported (ref. 118) without clinical manifestations.

Of the nematodes, lungworms of the genus *Filaroides* are commonly found in squirrel monkeys (ref. 4), but appear to cause little damage or respiratory embarrassment. On the other hand, filariasis in squirrel monkeys is characterized by fibrinous exudative peritonitis and pleuritis with adhesions in both cavities accompanied by heavy infections.

Trematodes are occasionally found in the intestinal tract of squirrel monkeys, but show no evidence of pathologic response.

In the acanthocephalus group, the thorny-headed worms *Prosthenorclis elongus* and *P. spirula* are frequently found in the intestinal tract (ref. 4). Bowel obstruction, perforation, and peritonitis are common sequelae. Cestodes have been described in squirrel monkeys, but no signs of pathogenicity have been reported.

Fatal infestations of toxoplasma have been reported in squirrel monkeys (ref. 119), apparently due to a lack of natural resistance. Chagas disease (*Trypanosoma cruzi*) has also been reported in squirrel monkeys, and the authors have stressed the importance of laboratory workers being alert to the risk of transmission of the agent by reduviid bugs or contamination with saliva (ref. 120).

The external parasites *Demodex* sp. have been recovered from hair follicles, as have *Andycotes greeri* and *A. lawrenci* (ref. 4). Heavy infections were believed to lead to secondary bacterial infections.

Periodontal abscesses have been shown to cause draining fistulas in the maxillary sinuses in squirrel monkeys (ref. 121).

It is the opinion of the authors of the present report that, with adequate attention to preflight quarantine and screening procedures, the disease entities to which the squirrel monkey is susceptible should present no serious difficulties in regard to the utilization of these animals in space-flight experiments.

## REPRODUCTION, LABORATORY CARE, AND CLINICAL MANAGEMENT

In addition to the increasing interest in the use of the squirrel monkey based on its taxonomic relation to higher diurnal primates and man, other logistical advantages which have been responsible for the increasing and widespread use of this species are the prospects of reproduction in captivity, cost and ease of handling in laboratory care and maintenance, and the increasing experience in clinical management of its diseases.

### REPRODUCTION

Knowledge of reproduction may be critical for the continued long-term use of nonhuman primates in biomedical research, since there is increasing danger that the importation of many Old and New World primates may be limited or terminated by embargo from exporting countries. Also, maximum utilization of any species in aerospace biomedical research will ultimately require subjects of known genetic and geographic origin, age, sex, and clinical condition. These criteria, particularly for small-sample research studies will ultimately also necessitate the establishment of domestic breeding colonies. Despite the increasing use of the squirrel monkey in laboratories around the world, reliable information on their reproductive physiology is still incomplete and controversial. Most studies will disagree on the length of the estrous cycle, with published values ranging from 6- to 25-day cycles (refs. 122 and 123). Examinations of vaginal cytology have indicated that cycle periods may be variable and correlated with local environmental conditions, since evidence of seasonal cyclicity exists in their natural environment and the birth periods usually occur from January to March (ref. 124).

Numerous aspects of the reproduction of the squirrel monkey are currently under active investigation to establish more reliable information on estrus, ovulation, pregnancy and viable offspring, mating activity, sexual receptivity, and presence of spermatozoa in vaginal smears and vaginal plugs are under careful scrutiny as indicators of reproduction. The absence of overt menses complicates the determination of estrous cycle length and pregnancy. There is still no reliable information on correlations among selected indicators and ovulation. It has also been suggested that noncoital stimulation in the squirrel monkey may induce ovulation (ref. 10).

The "fatted male" feature in the squirrel monkey is a characteristic reproduction feature, peculiar to the male squirrel monkey. This seasonal change coincides with the breeding season and maximal spermatogenesis, as detected by testicular biopsy (ref. 9). That this phenomenon is clearly testosterone dependent has been demonstrated. Castration of fatted males caused loss of the fatted conformation and marked weight loss while castration of nonfatted males resulted in proportionally less weight loss. The fatted state appearance has been restored in the castrate by treatment with testosterone cypionate. When not in the fatted state, the males generally do not associate with females and are treated aggressively if they approach them.

As with the estrous cycle, lack of overt menstruation causes uncertainty about the length of gestation in the squirrel monkey. Without time-mating data and/or a menstrual period, the time of conception can only be estimated. The most reliable estimates at this time are based on the time of birth after pairing a nonpregnant female with an appropriately "fatted male." On this basis, gestation periods of  $170 \pm 2$  days have been reported, based on two pregnancies of 169 to 172 days,

respectively (ref. 123). Others have reported pregnancies of similar length of  $165 \pm 5$  days, or  $165 \pm 7$  days. Lorenz *et al.* (ref. 10) report a shorter mean gestation of 162.6 days with a range of 152 to 168 days after pairing. This shorter period was determined in six pairs of animals housed in outdoor cages. Possibly the squirrel monkey's gestation period may have either a somewhat variable length, due to environmental factors, or a larger standard deviation than is presently calculable from the limited number of reasonably documented gestation periods.

Breeding and reproduction in the squirrel monkey are seasonal. An unusual but seemingly consistent pattern has been noted by several investigators regarding the seasonality of breeding and birth in squirrel monkeys. This is fairly dramatic in their natural environment where pregnant females are observed from October to January and newborn infants are observed local with their mothers from January to March. Various reports have indicated that under cold conditions, the Colombian and Peruvian squirrel monkeys are pregnant from October to January, with a peak birth season from January to March. *Saimiri* obtained from the Santa Cruz region of Bolivia have been observed in early pregnancy from August to September at the Delta Regional Primate Research Center. This seasonality shifts dramatically from the winter months to the North American summer months when these animals are maintained in captivity.

### Squirrel Monkey Reproduction at the Delta Regional Primate Research Center

Although information on breeding of the squirrel monkey is not comparable to information concerning the rhesus monkey, an increasing number of published and unpublished studies and clinical experience have validated the feasibility of establishing a successful breeding colony under seminatural conditions at the Delta Regional Primate Research Center (DRPRC). A breeding colony has been established during the past 3 yr and is housed in large screened outdoor cages. In winter months, shelter is provided in pens and heat zones are also maintained by the use of heat lamps. These environmental modifications and arrangements have resulted in a colony that has been in excellent health and an improving record of reproduction. Reproduction statistics for 1974 are as follows: From a total of 129 selected females, there were 74 pregnancies, 56 live births, 13 still births, and 5 abortions. The conception rate was 58 percent, the live birth rate was 78 percent, still births 17 percent, and abortions 5 percent. These reproductive statistics at DRPRC are a considerable improvement over 1973 and reflect increasing knowledge and skill in the management of the breeding colony. Careful records have also been kept on seasonal birth distributions. These records indicate that for 1974, the peak seasonal birth distributions occurred during the months of May and June, some births occurring with decreasing frequency during July and August.

A nursery has also been established at DRPRC to insure the rearing of infant squirrel monkeys under carefully controlled environmental conditions. Infant squirrel monkeys are removed from their mothers on the day of birth, isolated, and assigned to the nursery. At the age of 3 to 5 months they attain relative maturity and are assigned to specific research studies, or long-term projects. The interbirth period at DRPRC is currently a mean of 364 days. This period is less than has been reported by others. Since seasonality has been maintained in birth distribution at DRPRC, the removal of the infants from their mothers at birth appears to have had no demonstrable effects on the overall reproduction of healthy and viable squirrel monkey offspring.

## LABORATORY CARE AND CLINICAL MANAGEMENT

An extensive review has been published on the laboratory care and clinical management of the squirrel monkey (ref. 98). Only salient aspects need emphasis for optimum care and clinical management of the squirrel monkey as a suitable subject for biomedical research. Briefly, laboratory diets should include 25 percent protein, 8 percent fat, vitamins C and D<sub>3</sub>, and at least 100 mliter of H<sub>2</sub>O each day. Dental hygiene is very important since teeth become abscessed and result in draining fistulas from the maxillary sinus beneath the eyes. However, prophylactic, diagnostic, and therapeutic measures have been developed for the squirrel monkey at DRPRC. *Saimiri* often harbor various virus nonpathogenic to this species and of little consequence in the management of a healthy colony. Bacterial infections, a common cause of death, are generally secondary manifestations also avoidable with proper care and management. Clinical tuberculosis is rare and abdominal rather than pulmonary. Squirrel monkeys obtained from commercial sources are, with few exceptions, parasitized by numerous species of metazoan and protozoan parasites. However, few of these cause clinical symptoms or contribute to morbidity in carefully managed laboratory populations. Many species of parasitic organisms can be eradicated by drug therapy, if necessary. A combination of selection and treatment with anthelmintics can produce animals with few or no parasitic infections. Obviously, the most reliable conditions for obtaining squirrel monkeys of known origin, sex, age, and clinical state are to obtain them from a well-managed breeding colony.

### USE OF THE SQUIRREL MONKEY IN PREVIOUS AEROSPACE RESEARCH

For a variety of previously cited phylogenetic, logistical reasons and due to a rapidly increasing number of publications, the squirrel monkey has now become one of the most popular and widely used nonhuman primates in both basic and biomedical research (ref. 1). For the same phylogenetic, logistical reasons and the knowledge gained in connection with preparation for space flight in laboratory experiments, it was the first nonhuman primate introduced into aerospace biomedical research (ref. 2). In addition to the essential biological characteristics required or set by life-support systems, other major considerations in selection of an animal as a space-flight candidate are the basic knowledge contained in the literature gained by previous extensive laboratory experiments on that particular species. It is only against this background of reliable basic information that the anticipated reactions of the squirrel monkey under the various space-flight conditions can be compared with the animal's normal behavior, physiology, chemistry, and morphology. It is apparent from this review that considerable basic scientific information has been obtained on the squirrel monkey in terms of its behavior, unique brain/body ratio among primates, its small size and availability, and clinical status and in terms of an increasing number of studies that have been made in connection with preparation of squirrel monkeys for space-flight experiments. As stated in the introduction, the squirrel monkey has been utilized in actual bioflight missions, in acute laboratory experiments dealing with short-term effects of launch, recovery and simulated space-flight environments, and in chronic laboratory experiments designed to clarify risks to man in long-duration space missions. An extensive review has been published on the use of the squirrel monkey in aerospace biomedical research (ref. 2). The use of the squirrel monkey in previous aerospace biomedical research, listing the functions examined, the test conditions, and the major findings, is presented in table 12.

Until recently, research publications on the use of the squirrel monkey in space flight were obtainable only in widely scattered and not readily available references (ref. 2). In the above-cited reference, the published literature on the role of the squirrel monkey in space flights has been summarized in greater detail under the following test conditions: (i) Army-Navy bioflights; (ii) long-duration biospace flights; (iii) effects of high gravitational stress; (iv) effects of rotational forces on vestibular organs; (v) effects of high noise on organ of Corti; (vi) effects of high and low environmental oxygen, partial pressure, and ambient pressure; (vii) effects of cold and heat; and (viii) differential effects of strong magnetic fields.

From the selective review of the most relevant literature under the topics covered in this chapter, it can be concluded that the squirrel monkey does represent a distinct nonhuman primate "model," not only for basic and clinical research, but as a candidate for space-flight experiments. Obviously, the selection of any particular primate species for a space-flight experiment must be determined by the requirements and conditions of that particular experiment. Also, a comprehensive understanding of any one primate species is unlikely without reference to similarities and differences of other species within the primate order. The explicit or implicit comparisons of the biological characteristics of the squirrel monkey with other primate and nonprimate species provided in this selective space-flight review should provide compelling evidence that both basic and space-flight related knowledge can be interpreted ultimately more reliably where a broader phylogenetic perspective is used as a frame of reference.

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TABLE 1.— BODY AND ORGAN WEIGHTS OF ADULT MALE AND FEMALE SQUIRREL MONKEYS<sup>a</sup>

Body and organs <sup>b</sup> Weight (g, mg)	Male (n=17)		Female (n=8)	
	M.	S.E.	M.	S.E.
Body (g)	659.0	23.6	554.0	10.2
Brain (g)	26.4	.5	23.3	.5
Pituitary (mg)	19.5	1.1	27.2	1.1
Heart (g)	3.4	.2	3.0	.4
Lungs (g)	5.1	.5	4.5	.5
Spleen (g)	1.6	.5	1.6	.3
Liver (g)	18.9	2.6	16.3	2.1
Pancreas (g)	1.5	.2	1.3	.1
Adrenal (mg)				
Left	112.0	4.5	129.0	2.9
Right	107.0	4.0	117.0	5.2
Kidney (g)				
Left	1.8	.2	1.7	.1
Right	1.8	.1	1.7	.1
Testes (g)				
Left	1.2	.2	--	--
Right	1.4	.2	--	--
Ovaries (mg)				
Left	--	--	100.0	.0
Right	--	--	130.0	.0

<sup>a</sup>Weight values including means and standard errors were obtained from subjects born and raised in the author's laboratory and from published references.

<sup>b</sup>Biological sources of weight difference include age, sex, laboratory or geographic origin for subspecies and left-right laterality.

TABLE 2.— VISUAL FUNCTIONS IN THE SQUIRREL MONKEY

Function	Value	Test condition	Subjects
Acuity, min separable binocular	0.74 ±0.02 min of arc	Method of limits, diffraction gratings, 1 m, white light	9 3
Brightness, discrimination threshold	0.20 - 0.60 DI/I of log I -2 to +2	2-choice method targets, background	3
Color vision spectral sensitivity	trichromatic protanomaly 420-600 mμ	2-choice yellow-green green-blue green-red	4
ERG CFF retinal duplicity	15-20 Hz scotopic photopic crossover	Evoked ERG white colored light	8



TABLE 3.— EMETIC INCIDENCE — ROTATION TEST

Percent preoperative (latency)				Percent postoperative	
Random		Selected		Unilateral	Bilateral
45 <sup>a</sup> (7 min; n=11) 44.8 <sup>d</sup> (45 min; n=29)		100 <sup>b</sup> (8 min; n=6) 100 (35 min; n=3)		100 <sup>b,c</sup> (n=3) ---	0 <sup>b,c</sup> (n=3) 0 <sup>e</sup> (n=3)
Caloric threshold (±0.2° C)					
Percent preoperative		Percent unilateral 7 mo postoperative <sup>f</sup>		Percent bilateral 7 mo postoperative <sup>g</sup>	
Right	Left	Right	Left	Right	Left
34.6 <sup>a</sup> (n=11)	34.3 <sup>a</sup>	---	---	---	---
30.17 <sup>b</sup> (n=6)	30.2 <sup>b</sup>	33.0 <sup>b</sup> (n=3)	0 <sup>b</sup>	0 <sup>b</sup> (n=3)	

<sup>a</sup>Mean values (ref. 61)<sup>b</sup>Mean values (ref. 60)<sup>c</sup>Labyrinthectomy<sup>d</sup>Mean values (Brizzee, K. R., Klara, P., and Mehler, W. R. Effect of ablation of area postrema on emetic response to motion and 5-hydroxy-tryptophan in the squirrel monkey. Unpublished results.<sup>e</sup>Postrectomy<sup>f</sup>Left labyrinthectomy<sup>g</sup>Bilateral labyrinthectomy

TABLE 4.— TASTE AND OLFACTORY DISCRIMINATION IN THE SQUIRREL MONKEY

Function	Value	Test-condition	Subjects
Taste			
Glucose discrimination	DI/I percent conc.	paired comparison preference	4
Taster nontaster genetic-chemoreception	95 percent tasters	phenol-thio-carbamide taste polymorphism	14
Olfaction <sup>a</sup>			
Nutrition Reproduction Social organization Communication	microsmatic macrosmatic ?	pheromones scent marking territory	?

<sup>a</sup>Olfactory studies on olfaction of the squirrel monkey have not been reported.

**TABLE 5.— SENSORY, LEARNING, MOTOR PERFORMANCE TESTS USED FOR  
UNRESTRAINED AND RESTRAINED SQUIRREL MONKEYS**

Performance test <sup>a</sup>	Capacities
	<b>Unrestrained</b>
WGTA	Sensory discrimination; learning; delayed responses.
Operant conditioning	Sensory discrimination; learning; drives; arousal; correlative psychophysical-physiological-chemical-morphological multivariate studies.
Runways	Sensory discrimination; learning; drives; arousal.
Mazes	Spatial discrimination; curiosity.
Patterned string problems	Sensory discrimination; learning.
Rail test	Dynamic equilibrium.
Platform test	Equilibrium
	<b>Restrained</b>
Operant conditioning	Sensory discrimination; learning; drives; arousal; correlative psychophysical-physiological-chemical-morphological multivariate studies.

<sup>a</sup>Responses measured on all tests: speed, latency, frequency, intensity, complexity, stereotypes.

**TABLE 6.— ESTIMATED BASELINE OR NORMATIVE HEMATOLOGICAL VALUES OF ADULT MALE AND FEMALE SQUIRREL MONKEYS**

Constituents (Units)	Male <sup>a</sup>		Female <sup>b</sup>		Combined <sup>c</sup>	
	Mean	S.E.	Mean	S.E.	Mean	S.E.
Hemoglobin (g percent)	13.1	0.38	12.32	0.84	14.8	0.8
RBC (10 <sup>6</sup> /mm <sup>3</sup> )	5.1	.47	6.55	.60	8.3	.6
Hematocrit (percent)	45.7	2.64	38.95	1.1	46.9	2.4
WBC (10 <sup>3</sup> /mm <sup>3</sup> )	9.8	1.2	9.57	1.32	8.2	2.4
Lymphocytes (percent WBC)	51.3	3.7	48.46	4.93	51.9	13.7
Neutrophils (percent WBC)	47.3	3.5	50.31	7.17	46.3	13.8
Eosinophils (percent WBC)	.86	.45	6.85	.64	5.3	5.2
Basophils (percent WBC)	.28	.28	.1	.3	.3	.7
Monocytes (percent WBC)	.28	.18	1.5	.49	1.2	1.3

<sup>a</sup>The sample means and standard errors of the male hematological values were obtained from one single published reference.

<sup>b</sup>For the females, the sample means from 1 unpublished and 3 published studies were combined.

<sup>c</sup>The sample means and standard errors in the combined male and female values were obtained from a single and different published reference.

**TABLE 7.— ESTIMATED BASELINE OR NORMATIVE BLOOD CHEMISTRY VALUES OF ADULT MALE AND FEMALE SQUIRREL MONKEYS**

Serum chemicals (Units)	Combined	
	Mean	S.E.
Sodium (meq/l)	160	6.1
Potassium (meq/l)	5.6	1.2
Chloride (meq/l)	114	5.2
Calcium (mg percent)	10.2	.6
Phosphorus (mg percent)	5.3	1.4
Bilirubin (mg percent)	.2	.3
Glucose (mg percent)	72.0	20.0
Urea nitrogen (mg percent)	20.7	6.2
Cholesterol (mg percent)	199.0	34.0
Total protein (g percent)	7.3	.6
Albumin (g percent)	4.4	.3
BUN (mg percent)	21.0	6.7
LDH (I.U.)	229.0	66.0
Alk. phosphatase (I.U.)	110.0	55.0
SGOT (I.U.)	55.0	24.0
Creatinine (mg percent)	.4	--
Lactic dehydrogenase (U/mliter)	381.9	110.9

TABLE 8.— NUTRITION AND DIETS OF THE SQUIRREL MONKEY IN NATURAL HABITAT, LABORATORY AND RESEARCH

Natural habitat							
Buds, fruits, nuts, and insects as verified by examination of intestinal content							
Basal semipurified laboratory diet							
Constituent	g/100 ml	Vitamin mixture in dextrose <sup>a</sup>					
Casein	25	A	1250 IU	Alpha tocopherol	10 mg	Menadione	4 mg
Sucrose	61	D <sub>3</sub>	400 IU	Ca-pantothenate	3 mg	Thiamine	1 mg
Salt mixture	4	B <sub>6</sub>	1 mg	Ascorbic acid	50 mg	Niacin	4.9 mg
Corn oil	8	B <sub>12</sub>	2 µg	Folic acid	100 µg	Choline	500 mg
Vitamin mix in dextrose	2	Biotin	20 µg	Riboflavin	1 mg	Inositol	1100 mg
Pellet and liquid research diets							
Pellet	mg/tablet		Liquid			Percent	
Casein	57		Casein			33.3	
Confectioner's sugar	87.45		Sucrose			51.1	
Salt mixture	9.6		Cellulose (Alphacel)			5.6	
Avicel	57		Salt mixture			5.6	
Cottonseed oil	19.05		Vitamin diet fortification mix <sup>b</sup>			4.4	
Magnesium stearate	1.2						
Vitamin diet fortification mix <sup>c</sup>	7.5		Cottonseed oil			10 g	
H <sub>2</sub> O	Variable		H <sub>2</sub> O			50 ml	

<sup>a</sup>Unique feature of this diet is the requirement for vitamin D<sub>3</sub> (irradiated 7-dehydrocholesterol). Substitution of vitamin D<sub>2</sub> (irradiated ergosterol) is not sufficient.

<sup>b</sup>Comparable to basal diet vitamin mix.

<sup>c</sup>Obtained from Nutritional Biochemical Corporation.

TABLE 9.— GLUCOSE TOLERANCE LEVELS OF NORMAL AND IMPAIRED SQUIRREL MONKEYS<sup>a</sup>

Glucose tolerance test – mg glucose/100 mliter blood						
Animal group (n)	0 hr		1 hr		4 hr	
	Mean	S.E.	Mean	S.E.	Mean	S.E.
Normal (14)	51	2	105	6	59	2
Impaired (16)	56	2	171	11	76	4
Glucose tolerance – tolbutamide test – percent initial blood glucose						
Animal group (n)	20 min		30 min			
	Mean	S.E.	Mean	S.E.		
Normal (14)	63	5	54	5		
Impaired (16)	85	5	77	5		
Percent animals with glucose “impairment” – (# animals affected/# animals in group)						
Animal group	Juveniles		Adults			
	Percent male	Percent female	Percent male	Percent female		
Normal	72.73 (16/22)	72.09 (31/43)	42.45 (45/106)	62.52 (19/29)		
Impaired	27.27 (6/22)	27.91 (12/43)	57.55 (61/106)	34.48 (10/29)		

<sup>a</sup>These data were obtained from two separate publications.

TABLE 10.— RENAL FUNCTIONS IN THE SQUIRREL MONKEY<sup>a</sup>

Measurement (Unit)	Sexes combined	
	Mean	S.E.
Urine pH <sup>b</sup>	6.9	0.2
Urine volume (mliter/24 hr)	9.25	--
G. F. R. (mliter/min-g kidney (wgt))	.705	.035
Filtered H <sub>2</sub> O excreted (percent)	.99	.081
Filtered sodium excreted (percent)	.42	.093
U/P osmolality	3.51	.15
P <sub>osm</sub> (mOsm/kg H <sub>2</sub> O)	307	1.3
P <sub>Na<sup>+</sup></sub> (meq/l)	159	2.8
Renal cortex osmolality (mOsm/kg H <sub>2</sub> O)	372	23
Renal papilla osmolality (mOsm/kg H <sub>2</sub> O)	786	109

<sup>a</sup>Data from reference 99, unless otherwise indicated.<sup>b</sup>Data from reference 12.

TABLE 11.— DISEASE SUSCEPTIBILITY

Bacterial	Viral	Parasitic	Dental
Pasteurellosis Tuberculosis Salmonellosis Actinobacillosis	Arboviruses yellow fever dengue Herpesviruses H. tamarinus Cytomegalovirus Rabies Reovirus	Nematodes Filaroides Filariasis Trematodes flukes Acanthocephalus Cestodes Protozoa Trichomonad Plasmodium Toxoplasmosis Nosematosis Trypanosoma Demodex	Periodontal abscesses

TABLE 12.— USE OF SQUIRREL MONKEY IN PREVIOUS AEROSPACE BIOMEDICAL RESEARCH

Test conditions	Functions	Findings
Bioflights, acceleration deceleration weightlessness	EKG temperature respiration biosignals	adaptation tachycardia temperature stress
High gravitational stress centrifuge	behavior cardiac physiology equilibrium	no adverse effects behavior physiology
Rotating environments	vestibular organ	canal sickness
High intensity noise	cochlear cells	cell loss
Oxygen pressure	hyperoxia hypoxia	survival no CNS damage
Cold heat	behavior physiology	Acclimation heat-cold
Magnetic fields	behavior EEG	no adverse effects



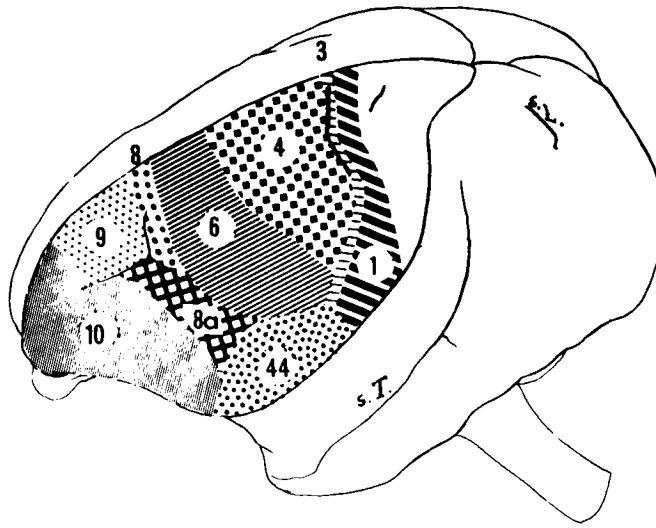


Figure 1.— Squirrel monkey brain viewed from lateral aspect showing central sulcus (CS) and Sylvian fissure (SF); perfusion-fixed with Bouin's fluid (ref. 13).

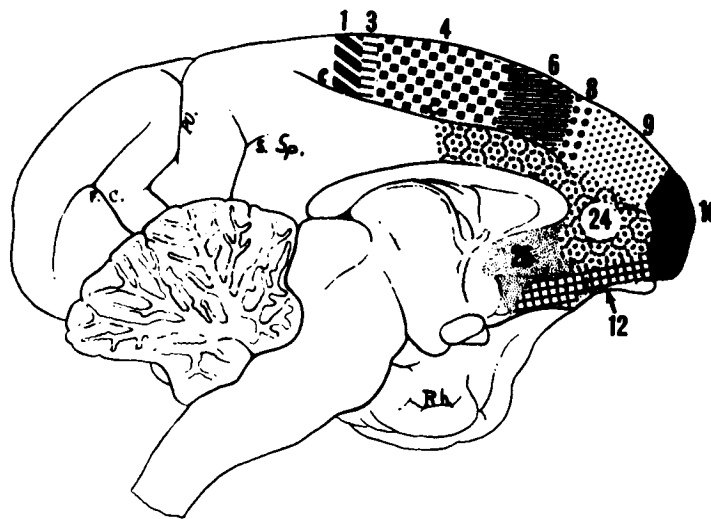


Figure 2.— Left cerebral hemisphere of squirrel monkey brain viewed from medial aspect; perfusion-fixed with Bouin's fluid (ref. 13).

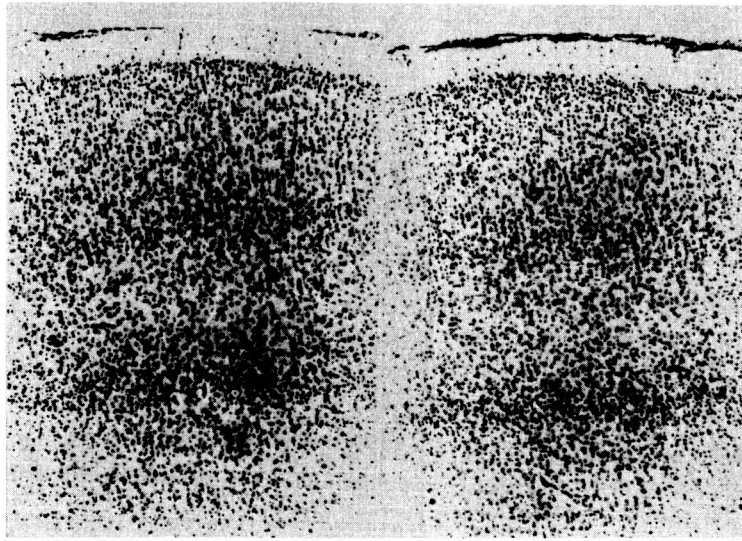


Figure 3.— Transverse section through visual cortex (area 17) of squirrel monkey showing characteristic cytoarchitectonic laminae;  $\times 600$ ; stain Cresyl violet.

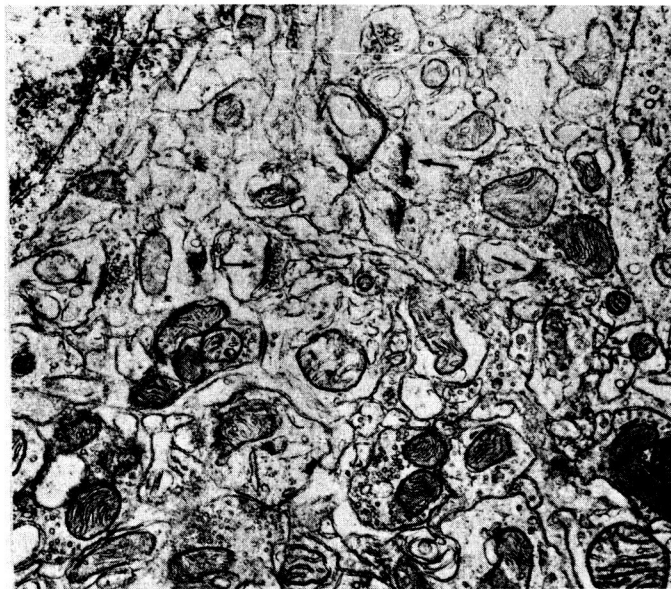


Figure 4.— Electron micrograph of lamina II of visual cortex (area 17) of squirrel monkey showing numerous axodendritic synapses in neuropil (arrows);  $\times 21,600$ ; stain lead citrate and uranyl acetate.

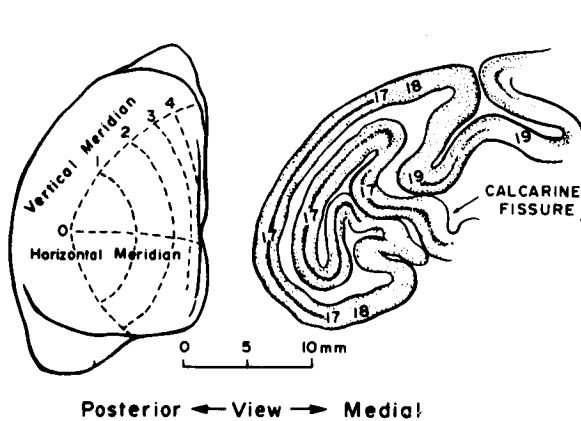


Figure 5.— Schematic representation of the retinal projection to lateral posterior and medial striate cortex of the left occipital hemisphere.

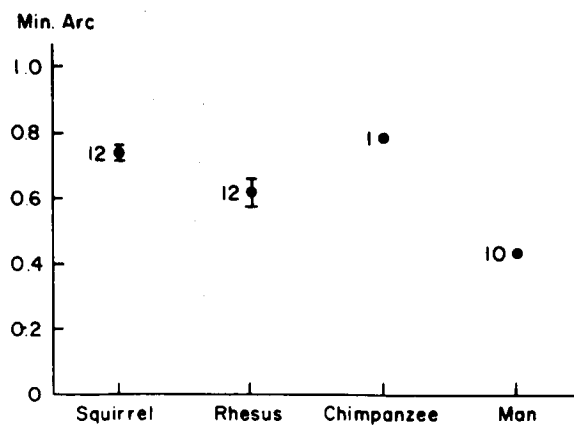


Figure 6.— Binocular minimum visible acuity of the squirrel and rhesus monkey, chimpanzee, and man. Numbers refer to the number of subjects in the sample of subjects tested. The values were obtained from published references cited in the text.

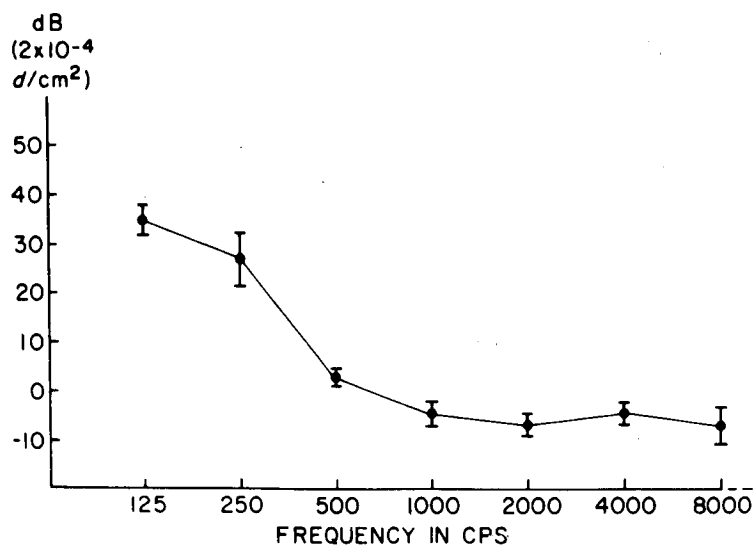


Figure 7.— Auditory threshold for the squirrel monkey based on the values from three adult subjects. The source for the auditory thresholds is cited in the text.

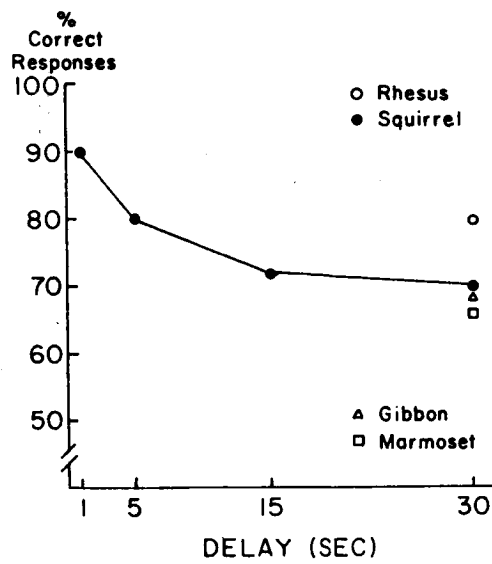


Figure 8.— Delayed-response performance of the squirrel monkey in relation to marmoset, gibbon, and rhesus monkey. Sources for the data are cited in the text.

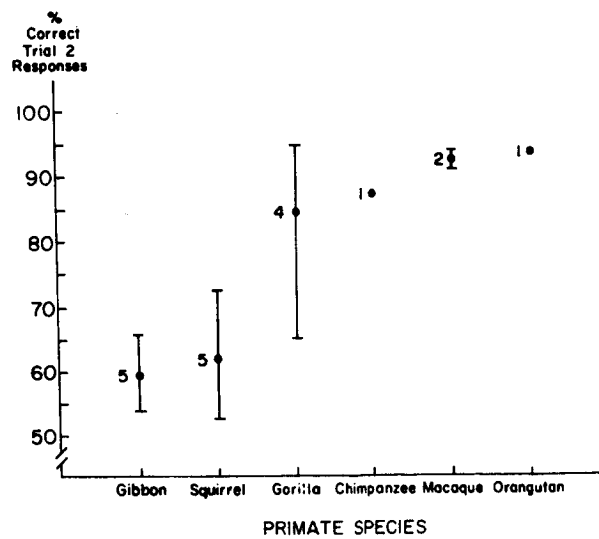


Figure 9.— Learning-set of the squirrel monkey in relation to other primates. Sources for data are cited in the text.

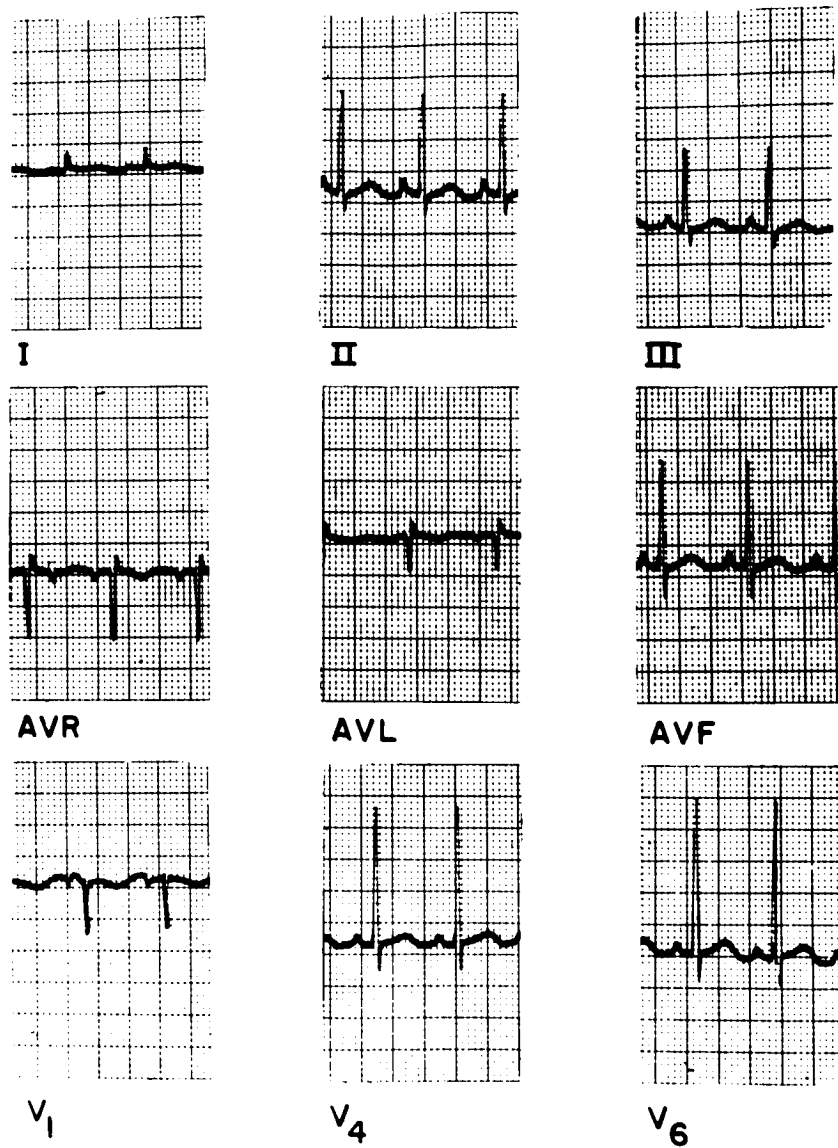


Figure 10.— A typical nine-lead ECG of a squirrel monkey. The paper speed was 50 mm/sec and the standardization was 1 in. V/cm. Reprinted with the permission of Dr. Robert H. Wolf.

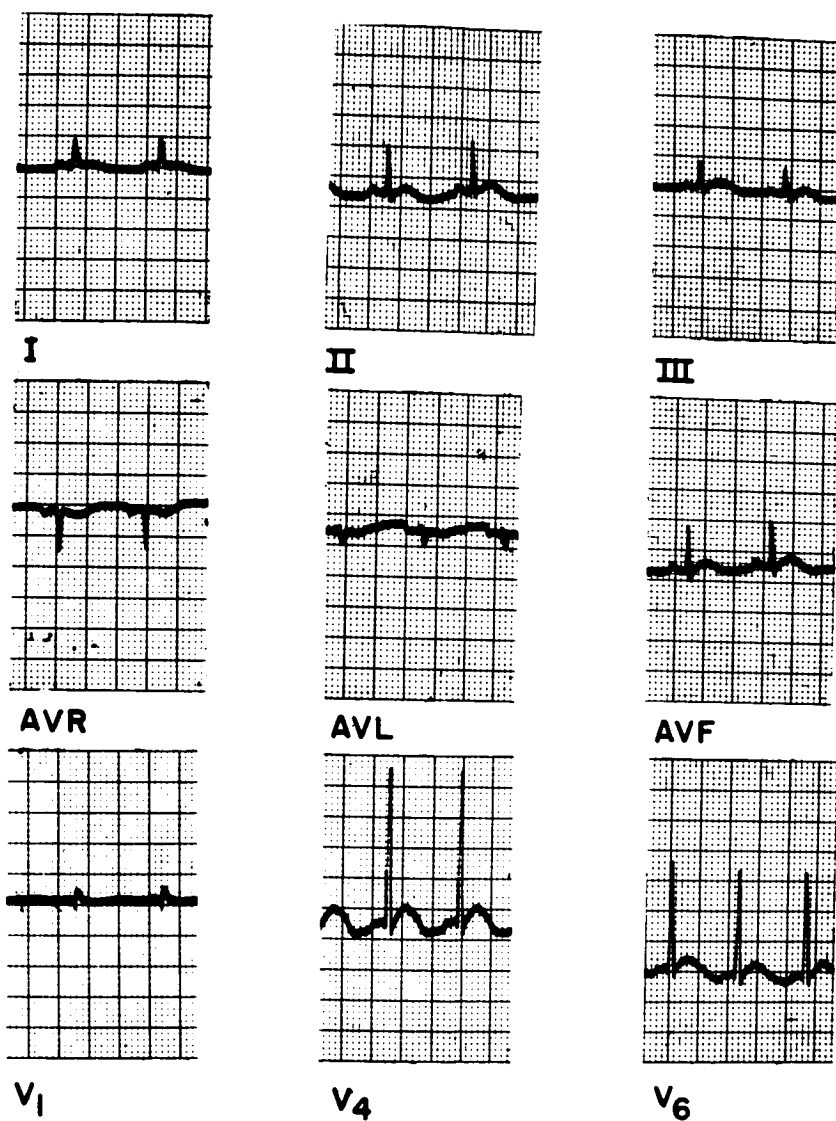


Figure 11.— A nine-lead ECG of a squirrel monkey with a serum calcium of 17.2 mg percent. The heart rate was 200/min and the QT duration was 0.12 sec in lead II. Reprinted with the permission of Dr. Robert H. Wolf.

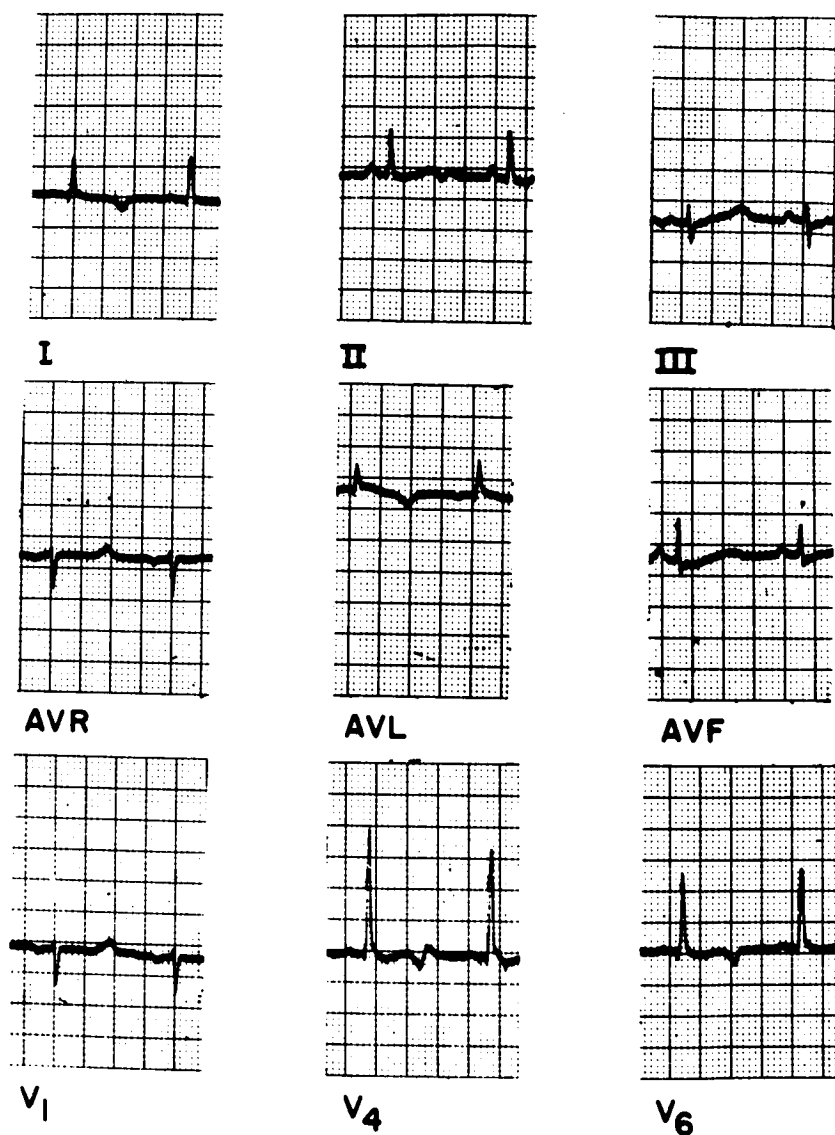
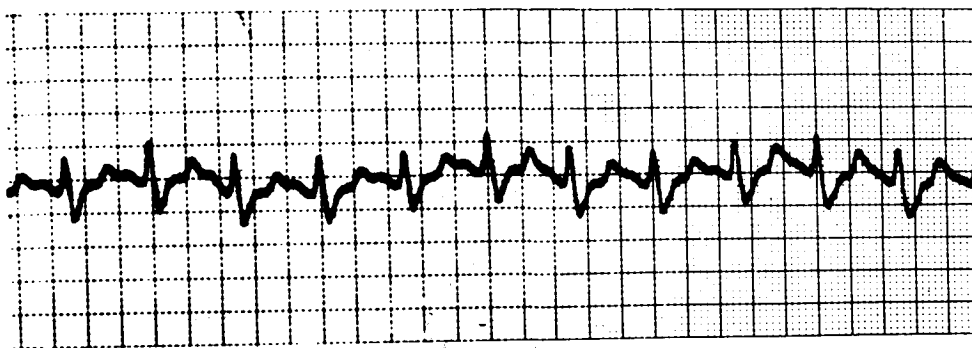


Figure 12.— A nine-lead ECG of a squirrel monkey in hypocalcemic tetany. The level of serum calcium was 5.2 mg percent. Discordant and diphasic T-waves were prominent. The rate was 160/min and the QT duration was 0.23-sec in lead II. Reprinted with the permission of Dr. Robert H. Wolf.

### Lead III



### Lead II

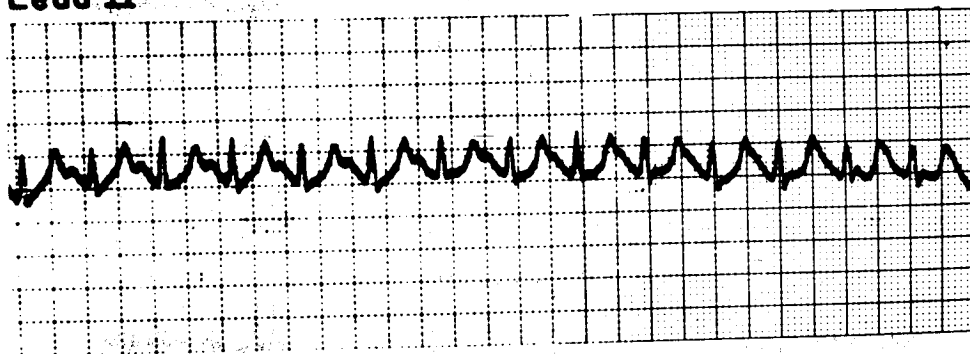


Figure 13.— Leads III and II of the ECG of a squirrel monkey showing depression and the loss of P-wave, and widening of the QRS complex during infusion of potassium. Reprinted with the permission of Dr. Robert H. Wolf.

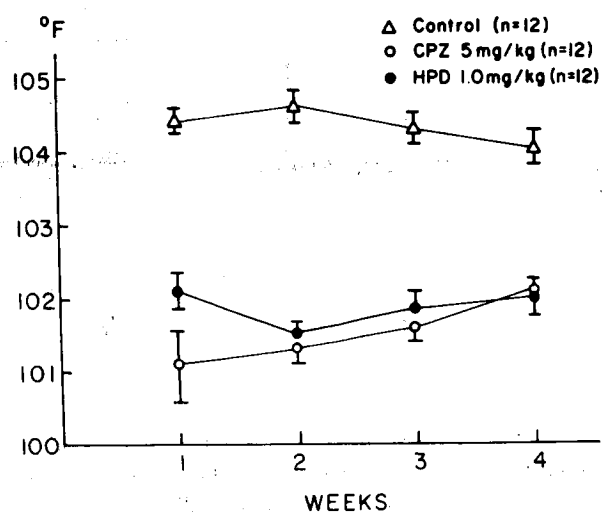


Figure 14.— Effects of CPZ (5.0 mg/kg) and HPD (1.0 mg/kg) on rectal temperature determined daily 1 hr after drug injection, extending over 4 weeks.



# THE CAPUCHIN MONKEY AS A FLIGHT CANDIDATE

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## INTRODUCTION

Selection of the most appropriate species of animal for a given experiment is, of course, influenced by a wide variety of considerations. Nonhuman primates are appropriate only for a relatively narrow range of studies, due to their relative high expense and the specialized facilities necessary for their maintenance. Many of the experiments in which the use of nonhuman primates is appropriate are focused on aspects of the nonhuman which are based on apparent similarities with man. The highly evolved nervous system and associated complex behavioral capabilities of the nonhuman primates make them good candidates for certain studies in the space environment since deleterious changes in these more complex aspects of a biological status can only be demonstrated by species which share such highly evolved features with man.

Nine years ago when we decided to extend our research in circadian rhythms to include a subhuman primate, we were faced with the problem of choosing one whose physiological regulation would be as close to that of man's as possible, yet would be small enough to make a good flight experiment candidate. The factors which we took into consideration in selecting such a candidate were aimed at keeping life support requirements and size and weight of the total package to a minimum allowing us the flexibility of flying more than one animal whenever possible. We also wanted an animal that tolerated confinement well and that was capable of providing us with as much information as possible about its physiological and behavioral function. This data might later be applied to man.

The rhesus monkey (*Macaca mulatta*) is a good candidate for a number of studies, since it has undoubtedly been more extensively studied than any other single monkey species and a large background of information about it already exists. Chimpanzees and baboons are also obvious choices for certain experiments, but concerns about large animal size, expense, and difficulties in maintenance, in some instances, may argue against their selection.

Figure 1 shows the candidate that we eventually selected, the capuchin monkey (*Cebus albifrons*). Cebus monkeys are of special interest because of their small size, their apparently high intelligence, and their relative disease resistance. They have several important assets which urge selection of this species for experiments in the space environment on the nervous system or processes under neural control such as homeostasis and adaptation, stress, behavior, etc.

## THE CAPUCHIN MONKEY

The capuchin or organ-grinder's monkey is relatively docile and easy to handle (with appropriate early experience and training) and has been a favorite pet for hundreds of years. Cebus monkeys are intelligent, trainable, relatively tractable, and survive well in intimate association with man.

Although monkeys of all types present a certain degree of health hazard to man, New World monkeys, such as the cebus monkey, present less of a hazard to man and are more disease resistant than Old World monkeys, such as the rhesus monkey. Approximately 10 percent of newly arrived rhesus monkeys have tuberculosis; the disease is rare in cebus. The serious (and often fatal) encephalitis (Binswanger's virus, Marburg virus, etc.) is also rare in cebus.

The capuchin monkey originates in the forests of South America, has done well in captivity, and has occasionally been bred (see table 1 for sources). It is small enough to be handled without sedation. These animals are compatible in groups so that housing is simplified. They are good feeders, quickly accepting purified diets. However, they do not survive fasting well, developing hypothermia, hypoglycemia, and becoming comatose (ref. 1).

Heinrich Kluver at the University of Chicago drew attention to the outstanding intellectual ability of cebus monkeys in the 1930's (ref. 2). He recently confirmed his conviction (personal communication) that this species is probably the most intelligent of the monkeys; their abilities, he reports, overlap with the anthropoid apes. More recent studies have supported this generalization.

As mentioned above, another favorable feature of capuchin monkeys is their relatively small adult size. Figure 2 shows growth curves for the animal. As adults, their weights range from 1.5 to 3 kg, while rhesus monkeys weigh from 5 to 8 kg for females and 8 to 14 kg for males (see table 2 for vital statistic information). This is a very distinct advantage of the capuchin monkey over most other primates since it enables the investigator to work with an adult animal as opposed to one that is developing. Thus, from a life support point of view, the capuchin monkey offers features that other species do not.

Figure 3 shows the cages in which they are housed. The cages are approximately 0.61 m (L)  $\times$  0.81 m (W)  $\times$  0.81 m (D) for two adults, whereas cages for rhesus males should be 1.22 m (L)  $\times$  1.07 m (W)  $\times$  1.14 m (D). Cages in which we have maintained one adult during research are 0.33 m (L)  $\times$  0.33 m (W)  $\times$  0.38 m (D) or 0.04 m<sup>3</sup>.

Considerable work has been done on the nutritional requirements of this monkey (ref. 1). In the natural state, it is an omnivore. Under laboratory conditions, it eats a prepared diet in pellet form (see table 3). The usual intake of an adult animal weighing 1.5 to 3.5 kg is between 30 and 60 g of this diet daily. One hundred and fifty pellets provide 550 kcal/day which compares well with its expected energy consumption of 115 to 332 kcal/day. It requires about 250 ml of water/day and puts out 70 to 100 ml of urine/day (range: 32 to 150 ml/day).

All of these factors plus lower volume requirements for most other life support systems, for example, oxygen, contribute towards minimizing the weight and size of the total flight package. In addition, the low urine output (as compared to the macaque that puts out 3 to 4 l/day) simplifies

the waste disposal system; or in the case where we wish to collect and preserve the urine for later analysis, absorption on a moving belt of some type becomes more feasible.

Cebus monkeys have been useful models for man in a variety of research areas. Figure 4 compares blood chemistry profiles for these monkeys and for man. It can be seen that the animals compare very closely to man in most parameters but show higher BUN, LDH, and SGOT, as do other subhuman primates.

Table 4 shows data from *Cebus albifrons* for some of the endocrine systems involved in the maintenance of homeostasis and vasomotor tone. Like man, the cebus adrenal puts out predominantly cortisol. Circulating levels are similar to those of man, in contrast to the squirrel monkey whose circulating corticosteroid levels are 20 to 100 times greater than man or other subhuman primates (ref. 3). Excretion of cortisol and catecholamines is also similar, and studies on the regulation of pituitary hormones and of the synthesis of epinephrine by the adrenal medulla indicate further similarities (ref. 4).

## INSTRUMENTATION AND DATA COLLECTION

Recognizing the versatility of the research potential of this animal as a flight candidate, our objective over the years has been to develop instrumentation and techniques to obtain information from as many systems as possible from a single unrestrained animal and to develop a flight experiment model and package that could be used for a variety of research objectives.

The decision to use an unrestrained animal was based on several considerations. Restraint drastically alters the physiological baseline (ref. 5), interferes with thermo-regulation (ref. 6), and sensitizes an animal to additional stresses, thus introducing a complicating variable into any of the data obtained. The main disadvantage of an unrestrained subject would be the limitation of obtaining blood samples inflight.

The effects of prolonged restraint in subhuman primates and other species have been extensively reviewed by Smith (ref. 7). Restraint initiates a severe physiological stress mediated via the hypothalamus-adrenal complex involving both the adrenal cortex and adrenal medulla. The most characteristic changes of chairing or couch-restraining monkeys for periods exceeding 1 week include anorexia and progressive loss in body mass (refs. 8, 9), increased excretion rates of nitrogenous compounds such as creatine and creatinine (ref. 9), marked decrease in bone mass, which is not affected by dietary mineral content (refs. 10, 11), increased calcium excretion and increasing muscle weakness (ref. 12). Banerjee (ref. 5) has found that cage restraint in monkeys leads to a progressive increase in the arterial alveolar oxygen tension gradient from an initial 2 mm to 21 mm Hg after 10 months. This is largely the result of a decreasing arterial saturation and was interpreted as resulting from a progressive unevenness of ventilation and perfusion induced by physical inactivity. One of the most common disabilities of long-term restraint is a disorientation which has been reported in a variety of species, including monkeys (ref. 13), which persists for some time after release from restraint. Although monkeys are considered to "adapt" to long-term restraint as evidenced by the return of circulating cortisol and other hormone levels to normal (refs. 12, 13), such adaptation cannot be considered equivalent to normality since other metabolic changes continue, the animals are hypersensitive to additional stress stimuli and drugs such as

barbiturates (ref. 14), and show a decreased ability to thermoregulate in response to changes in the environment (ref. 6). As an example, the changes in daily body temperature (BT) brought about by chair-restraining a macaque monkey are shown in figure 5.

It is obvious that a great number of the effects of restraint are similar to those produced by weightlessness and that one is dealing with an animal where the physiological baseline has been altered and is continuously changing. For these reasons we decided against using a restrained monkey as our flight animal.

With the development of advanced bioinstrumentation techniques, we have reached a level of sophistication in the monitoring of an unrestrained primate that was not previously possible. The multiplicity of parameters that we now can record continuously in these unrestrained animals with bioinstrumentation or techniques developed mostly at Ames Research Center is shown in figure 6. These include deep body temperature (DBT) from 1 to 4 sites, heart rate (HR), and electroencephalograph (EEG) for monitoring sleep stages. The EEG's are obtained using four leads from surface electrodes secured to the skull. Figure 7 shows the dimensions of the transmitters that we are using. All information is transmitted by telemetry from surgically implanted transmitters. In addition, the animals have been taught to perform various behavioral tasks, and locomotor activity is presently recorded using strain gauges in the base of the cages. Instrumentation for monitoring gastric pH and motility is also being developed.

We have also collected urine in fractional pools throughout the 24-hr period for several days from these unrestrained animals (fig. 8). These urine fractions are being analyzed for electrolytes, hormones, and other metabolic indices. The results will form the data base for the capuchin monkey for purposes of reference and to compare to values obtained by other techniques of urine collection and preservation, more appropriate to spaceflight, as they are developed. We have maintained animals instrumented in this manner for as long as 1 year.

Although we have used these instrumented animals primarily for circadian rhythm research, they readily lend themselves to a variety of experiments including behavior, sleep, nutrition, neuroendocrinology, calcium metabolism, pharmacology, and others. Cebus monkeys have been used in pharmacokinetic studies — being closer to man, for instance, in their metabolism of salicylates than the rhesus monkey. In addition, a good brain atlas exists for CNS work (ref. 15), and the cebus has been used in behavioral research, too.

From a nutritional point of view, the vitamin requirements are quite like those of human beings with the notable exception of vitamin D. The capuchin monkey, like other New World monkeys, appears to require natural vitamin D — that is, vitamin D<sub>3</sub> or cholecalciferol (refs. 16, 17). However, it should be emphasized that during these studies the animals had no exposure to either sunlight or ultraviolet sources. The sensitivity of the cebus bone metabolism to vitamin D<sub>3</sub> and possibly ultraviolet make it an interesting model for the study of calcium metabolism. Cebus monkeys occasionally show gallstones which can lead to death. Cancers of various types have sporadically been reported in these animals. They will develop hypercholesteremia with certain dietary conditions and extensive atherosclerosis. However, myocardial infarctions have never been reported.

It therefore appears that cebus monkeys bear close similarity to man in most physiological, nutritional, and behavioral systems. Those differences that do exist could be exploited to answer

specific questions in the space environment. The life support requirements, the size and weight of the total package, the flexibility that the bioinstrumentation and other monitoring techniques can provide, and the considerable data base already obtained all contribute to their usefulness.

Finally, the capuchin monkey offers unique characteristics of size, intelligence, adaptability, and general health that make it a highly desirable flight candidate.

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#### TABLE 1.— SOURCE INFORMATION

1. 68,000 monkeys bought, sold or bred in U.S.A. in 1969.
2. 1059 cebus monkeys were in the above group or 1.6 percent.
3. 68 cebus monkeys were of breeding stock in U.S.A.
4. The following is a partial list of suppliers for cebus monkeys:
  - a. Blue Ribbon Pet Farm, 14300 S.W. 86th Ave., Miami, Fla. 33155.
  - b. Charles P. Chase Co., Inc., 7330 N.W. 66th St., Miami, Fla. 33166.
  - c. Alton V. Freeman, Spruce Pine, N.C. 28777.
  - d. International Animal Exchange, Inc., 1489 E. Nine Mile Rd., Ferndale, Mich. 48220.
  - e. The Pet Farm, Inc., 3310 N.W. South River Dr., Miami, Fla. 33142.
  - f. Rider Animal Co., Inc., R.R. 2, Box 270, Brooksville, Fla. 33512.
  - g. Shamrock Farms, Inc., R.D. 2, Middletown, N.Y. 10940.
  - h. Tarpon Zoo, Inc., P.O. Box 847, Tarpon Springs, Fla. 33589.
  - i. Tote Em In Zoo, Rte. 2, Box 368, Wilmington, N.C. 28401.
  - j. Trefflich's Inc., Whitehouse Station, N.J. 08889.
  - k. Woodard Asiatic Corporation, P.O. Box 8125, International Airport, San Francisco, Calif. 94128.

TABLE 2.— CEBUS MONKEY INFORMATION

1. Vital statistics:  
 Body weight: male (1150 to 3320 g)  
 Body length: male (320 to 565 mm), female (323 to 480 mm)  
 Tail length: male (342 to 560 mm), female (290 to 510 mm)  
 Longevity: maximum = 40 years, average unknown  
 Gestation period: 180 days  
 Chromosome diploid No.: 54  
 Normal HR: 185              BT: 37° C              Respiration rate: 28/min
2. Water consumption:  
 Expected: monkeys consume 1179 ml/m<sup>2</sup> body surface per day. For cebus monkeys, this is about 100 to 250 ml/day.  
 Measured: about 250 ml/day per monkey
3. Food consumption and diet:  
 Recommended feeding once per day.  
 Expected energy consumption: monkeys consume 100 kcal/kg per day. For cebus monkeys, this is about 115 to 332 kcal/day.  
 Measured food consumption: (monkey pellets, 11.1 mm × 9.5 mm, 750 mg each).  
 Maximum: 250 pellets/day; average: 150 pellets/day = 550 kcal/day.
4. Urine production:  
 Average: 70 to 100 ml/day  
 Range: 32 to 150 ml/day
5. Cage information:  
 Acceptable size: 0.61 m × 0.81 m × 0.81 m (2 adults) = 0.40 m<sup>3</sup>/monkey  
 Presently used size: 0.33 m × 0.33 m × 0.38 m (1 adult) = 0.40 m<sup>3</sup>/monkey
6. Light intensity:  
 Cebus monkeys have been studied in light intensities ranging from 1.3 to 160 fc (0.1 to 2.2 mW/cm<sup>2</sup>), the most common being 70 fc.

TABLE 3.— DIETARY REQUIREMENTS /100 g DIET<sup>a</sup>

Casein (vitamin-free)	20 g
Sucrose	59 g
Salts (Phillips and Hart)	.4 g
Corn oil	15 g
Cod liver oil (USP)	.2 g
Thiamine HCl	.2 mg
Riboflavin	.2 mg
Pyridoxin	.2 mg
Ascorbic acid	90 mg
Ca pantothenate	.6 mg
Niacin	.9 mg
Choline Cl	.175 mg
Inositol	10 mg
Folacin	0.2 mg
Biotin	0.003 mg
<i>p</i> -Aminobenzoic acid	10 mg
Menadione	4.5 mg
Vitamin A	1800 IU
Vitamin D <sub>3</sub>	.200 IU
α-Tocopherol	10 mg
Vitamin B <sub>12</sub>	27 μg

<sup>a</sup>Experimentally determined an adequate diet for cebus monkeys during growth, pregnancy, lactation, and adult life (ref. 1).



TABLE 4.— ENDOCRINE AND NEUROTRANSMITTER DATA IN *Cebus albifrons*

Tissue	PNMT	Epinephrine	Norepinephrine	ACTH	Hydrocortisone
Brain					
Olfactory bulb	—	24.01 $\mu$ g/g	40.0 $\mu$ g/g	—	—
Olfactory tubercle	—	0.48 $\mu$ g/g	2.72 $\mu$ g/g	—	—
Anterior pituitary (wt = 22.4 $\pm$ 2.3 mg)	—	—	—	55.01 mU/mg	—
Plasma	—	—	—	1.9 to 2.8 mU/100 ml	21.64 $\pm$ 2.1 $\mu$ g/100 ml
Urine	—	5.0 $\mu$ g/24 hr	2.0 $\mu$ g/24 hr	—	28.8 mg/24 hr
Adrenal <sup>a</sup> (wt = 202.5 $\pm$ 7.8 mg)	20.3 $\pm$ 1.1 nmol/gland/hr	49.0 $\pm$ 1.7 $\mu$ g/gland	1.1 $\pm$ 0.05 $\mu$ g/gland	—	21.5 $\pm$ 0.7 $\mu$ g/g

<sup>a</sup> Steroid hormone profile in adrenal cortex of cebus monkeys:

Hydrocortisone (Cpd F)	13.7 to 29.3 $\mu$ g/g tissue
11-Deoxyhydrocortisone (Cpd S)	9.4 to 10.9 $\mu$ g/g tissue
Corticosterone (Cpd B)	1.1 to 2.5 $\mu$ g/g tissue
11-Dehydrocorticosterone (Cpd A)	<0.1 $\mu$ g/g tissue
11-Desoxycorticosterone (DOC)	1.7 to 3.0 $\mu$ g/g tissue
Aldosterone	<0.1 $\mu$ g/g tissue



Figure 1.— The capuchin or organ-grinder monkey, *Cebus albifrons*.

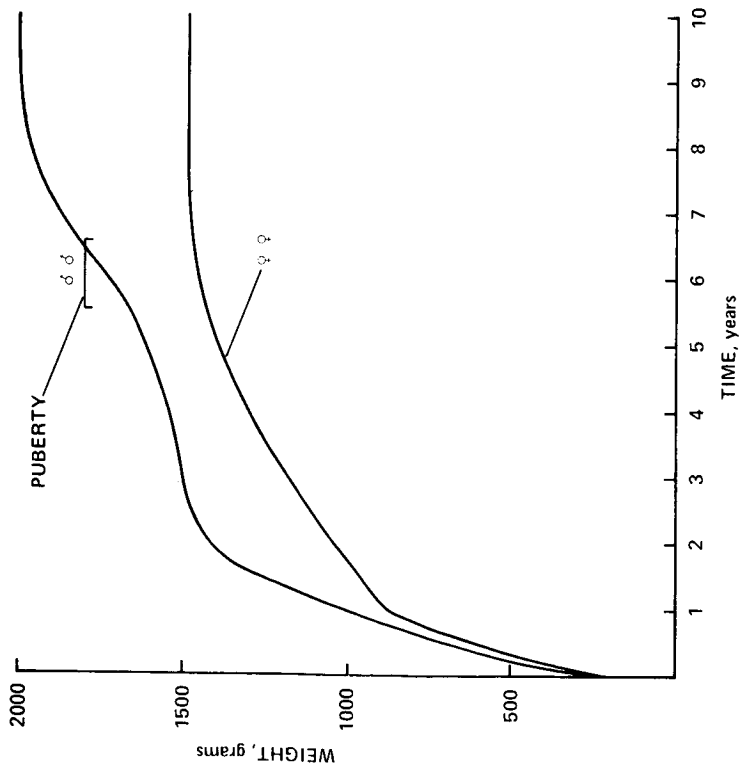


Figure 2.— Growth curves for male ( $\delta$ ) and female ( $\varnothing$ ) *Cebus albifrons*.

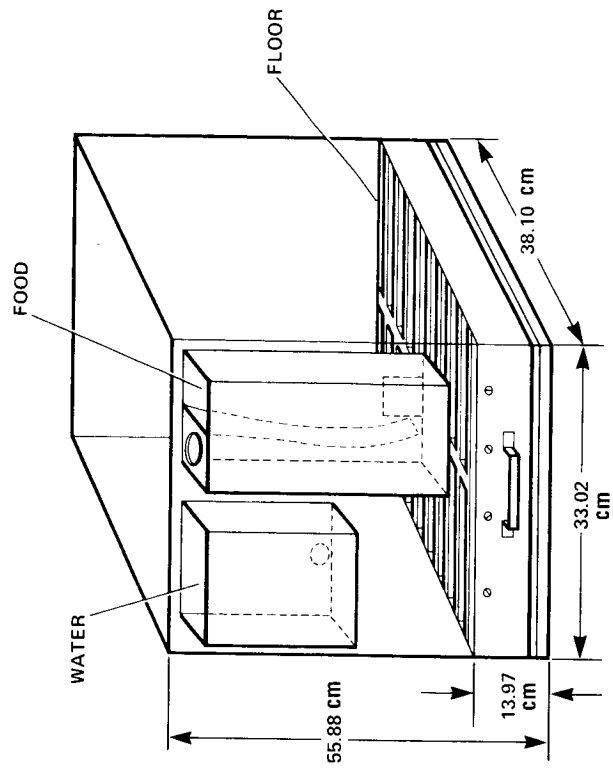


Figure 3.— Cage dimensions for *Cebus albifrons*.

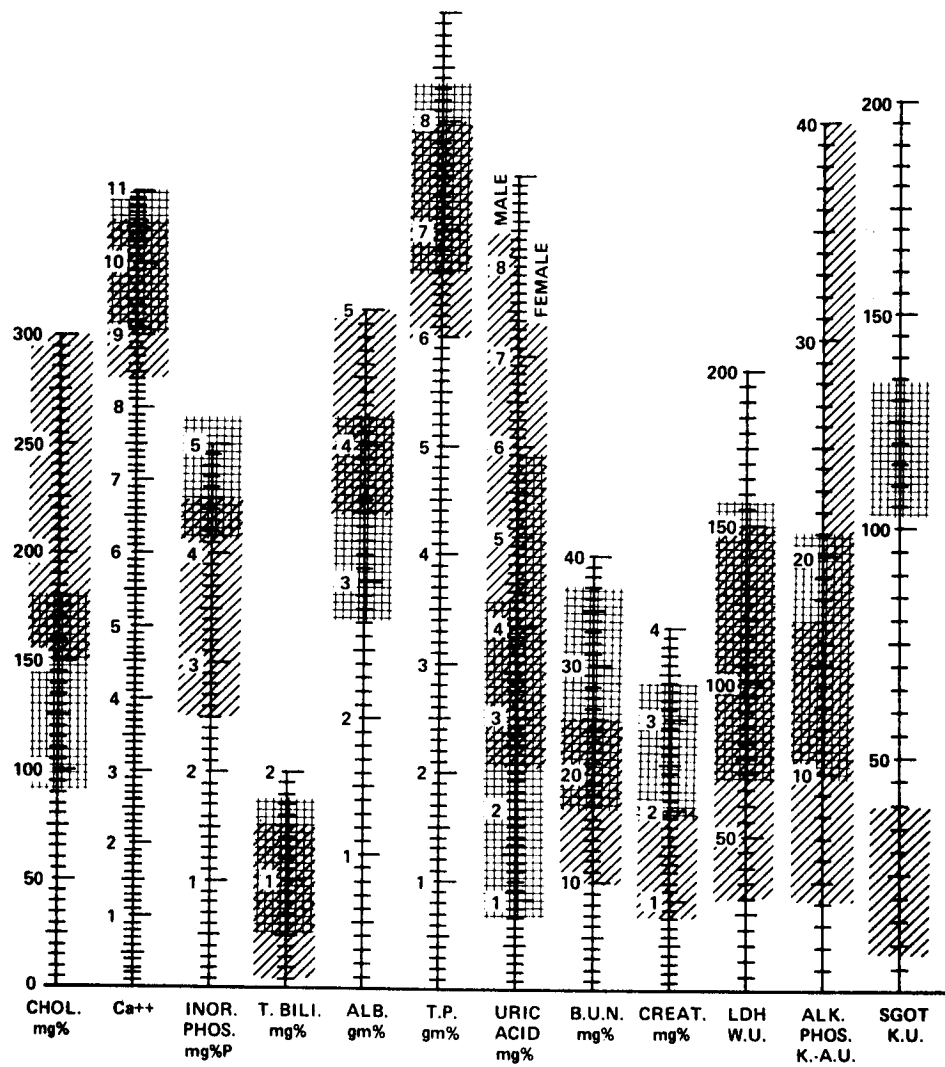


Figure 4.— Comparison of SMA-12 data for cebus monkeys and for man.

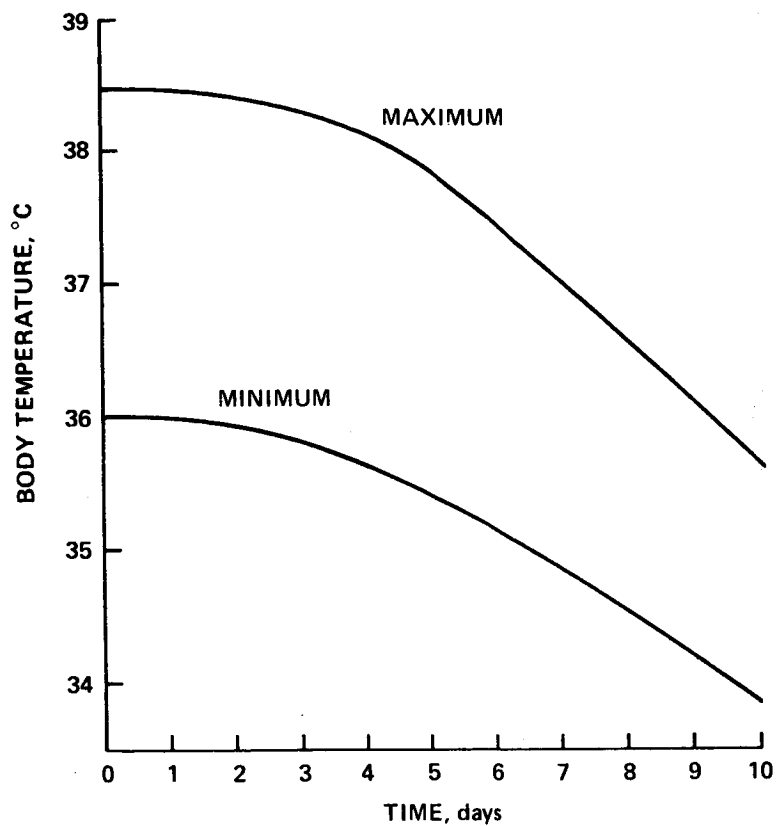


Figure 5.— Body temperature decrease associated with restraint of *Macaca nemestrina*.

## REPHASING OF DAILY RHYTHMS PHASE I

12 ON - 12 OFF LIGHTING REGIME

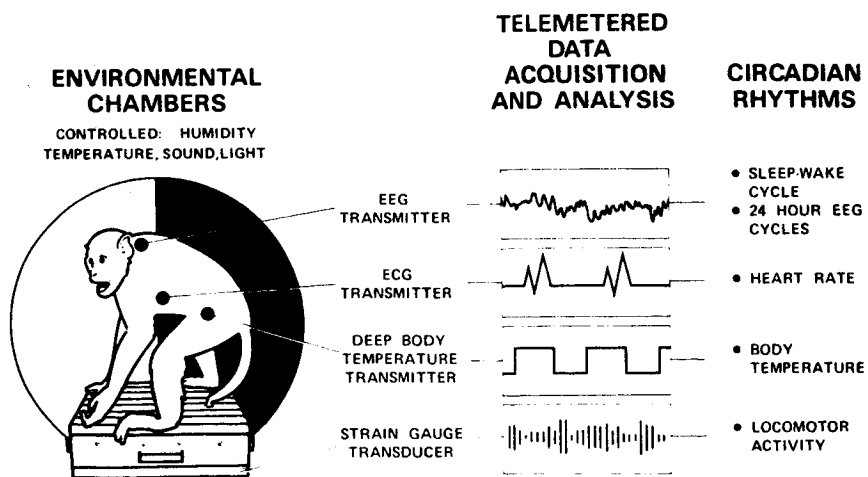


Figure 6.— Parameters obtained from unrestrained cebus monkeys by telemetry techniques.

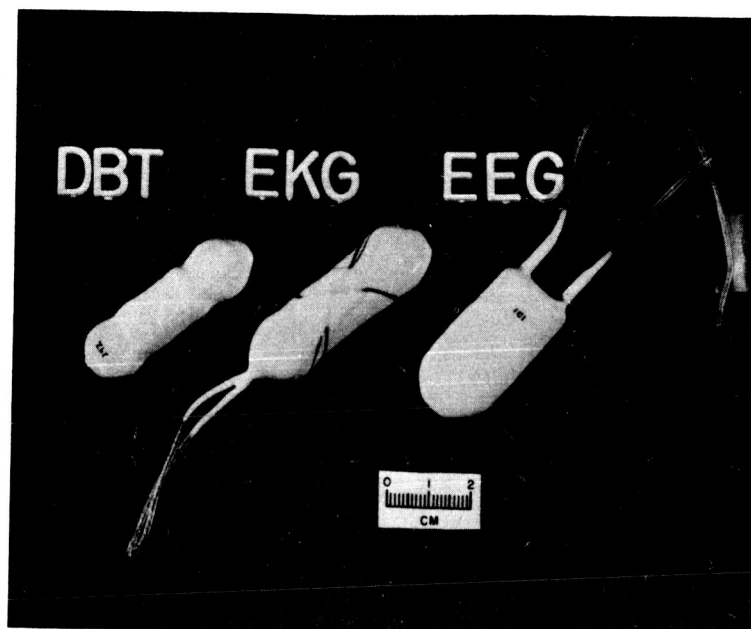


Figure 7.— Implantable telemetry units for recording deep body temperature, EKG, and EEG, showing actual dimensions.

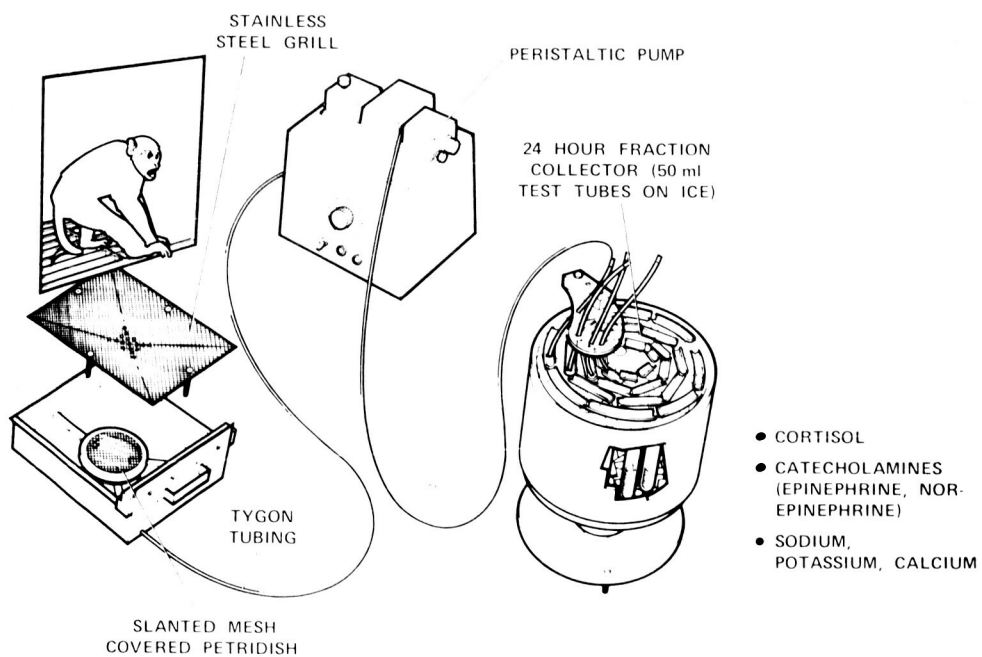


Figure 8.— Urine collection and analysis equipment for unrestrained cebus monkeys.

# THE PIG-TAILED MONKEY (*Macaca nemestrina*) AS A SPACE-FLIGHT CANDIDATE

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## INTRODUCTION

The complementary use of both human and animal subjects to study environmental physiology has been practiced for a number of years in our laboratory. In common with many physiologists, we have used a wide array of animal species in our research, ranging from mice through rats, hamsters, guinea pigs, rabbits, raccoons, dogs, seals, and miniature swine.

About 15 years ago, we became interested in the possibility of using unanesthetized monkeys to study the nature of the cardiovascular and respiratory adaptations that occur in man when he stays at high altitude for long periods of time. Our interest was prompted by the fact that the research required the use of chronically implanted vascular catheters in the pulmonary artery and the aorta, which would not have been feasible in human subjects, and we wanted an adult animal whose cardiovascular responses approximated those of man more closely than do those of the nonprimates.

The study also required that we take repeated blood samples during a period of many weeks. Thus, in order to avoid the complication of excessive blood loss from the experimental animals, it was necessary to select an animal whose total blood volume was large in comparison to the volume of blood to be removed during the study. At the same time, practical considerations dictated that the size and strength of animal should be within manageable limits in terms of the resources of our laboratory. This matter of conflicting experiment requirements, incidentally, is not an uncommon kind of problem for the physiologist and, in the parlance of the engineer, the various trade-offs must be considered in selecting the optimal species of animal to investigate a particular research problem.

## PRIMATE SPECIES CONSIDERED

After a careful survey of the literature and of the commercial availability of primate species, and after consultation with several experienced primate physiologists, anthropologists, and psychologists, we chose five species as possible candidates for our program. These were: *Saimiri sciurea*, the squirrel monkey; *Cebus apella*, the brown capuchin monkey; *Macaca mulatta*, the rhesus monkey; *Macaca arctoides*, the stump-tailed macaque; and *Macaca nemestrina*, the pig-tailed monkey, or giant rhesus.

We also seriously considered the chimpanzee, *Pan troglodytes*, as a candidate. However, on good advice, it became apparent that the adult, male chimpanzee requires highly specialized and costly handling procedures and facilities that were completely beyond our financial resources. The juvenile chimpanzee, such as Ham and Enos of Mercury Program fame, was more manageable but

suffered the serious disadvantages of rapid growth during the expected time-course of our experiments and the physiological liabilities of preadolescence and adolescence. Therefore, we chose to eliminate the chimpanzee as a possibility, despite its position as perhaps the most phylogenetically proximate primate to man, and subsequent visits to the chimpanzee research facility at Holloman Air Force Base in New Mexico confirmed the practicality of our decision.

Representatives of the five species we had settled on were obtained and studied for 1 to 2 yr with respect to temperament, amenability to training and restraint, handling characteristics, surgical tolerance, cage breeding, and physiological characteristics. At the end of this time, it was concluded that although the *Saimiri* and the *Cebus* had some good features they were basically too small for the experiments we had in mind. Full-grown squirrel monkeys weigh about 1 kg, and the capuchin about 3 kg. Also, the very long, prehensile tail characteristic of both these species represented a major problem in experiments involving long-term seated restraint. The tail length of the capuchin is about equal to head plus body length, and the squirrel monkey tail is about half again as long as head plus body.

Among the three macaques we had selected for study it rather quickly became evident that *Macaca nemestrina* was significantly superior to the rhesus and stump-tailed macaques in most criteria of importance to our research, so we decided to choose the pig-tailed monkey as a surrogate for man in our work. Our decision was reinforced by the papers of the Oxford experimental psychologist, J. Cole (refs. 1 and 2) in praise of *Macaca nemestrina* as an experimental subject, which were published at about that same time. I take the liberty of quoting from page 106 of his 1963 paper, courtesy of the author and the Zoological Society of London:

"... To the English of the Straits Settlements they are known as pig-tail or coconut monkeys, the latter name being derived from their use by the natives for gathering coconuts. The Malays catch these monkeys when a year or two old and bring them up in the family, teaching them, as a hill shepherd teaches his dog, to obey a considerable number of words of command which are used to control and direct the monkey when coconut picking.

"It was because we were aware of this capacity to respond to training that we chose this monkey in preference to the more generally used *M. mulatta* for study in this laboratory.

"We have worked with both species, and found that for docility and ease in handling and training the *M. nemestrina* is far superior to the *M. mulatta*, particularly as it was desired to achieve the animal's cooperation and avoid the more forceful and traumatic methods of training..."

Cole (ref. 2) goes on to point out that, viewed macroscopically, as seen in figure 1, the brain of *Macaca nemestrina* is somewhat more convoluted than that of *Macaca mulatta* and somewhat less so than that of the East African baboon, *Papio anubis*, especially in the areas of the occipital and parietal lobes. He also says that, histologically, there is some evidence that the cell layers in the gray matter of the sensory-motor area adjacent to, and within, the central sulcus are deeper in *M. nemestrina* than in *M. mulatta*.



Finally, quoting from page 109 of Cole's 1963 paper:

" . . . Active curiosity is highly developed, as in other monkeys, but the pig-tail appears to have a quality of patient concentration and perseverance when investigating a strange object, especially one that can be manipulated, that is less marked in the more impatient *M. mulatta* or in the destructive baboon. For this reason they are highly suitable for laboratory work as they will persist longer without frustration than *M. mulatta* and are far less aggressive toward apparatus than the baboon. Pig-tails are excellent subjects for training and testing on any work involving oculo-motor-sensory skills with the hand, not because their movements are more rapid than those of other monkeys, . . . but because they are more delicate, less hasty and more patient . . . "

Taking into account our own experience of the past 15 years with monkeys, both at high altitude and in space-flight experimentation, together with the experience of other laboratories that have compared characteristics of the three species of macaques most commonly used in physiological research, I have prepared a grade transcript for the three, much as we do for students at Berkeley, which is shown in table 1. On the basis of the 14 criteria listed, it may be concluded that more work is needed before the stump-tailed macaque is considered for space-flight experiments. The rhesus monkey receives a passing grade record, but the pig-tailed monkey graduates with honors. The overall grade-point average of *Macaca nemestrina*, incidentally, is not quite good enough to get into medical school these days, but it is acceptable for graduate work.

### BIOSATELLITE III EXPERIENCE

While there is a large measure of subjectivity in all of this, one unique major point can be made in favor of *Macaca nemestrina* as a space-flight candidate: it is the only nonhuman primate, other than the juvenile chimpanzee Enos who flew in Mercury 5 for 3.3 hr in 1961, that has flown in Earth orbit to date. This was the male pig-tailed monkey, Bonny seen in figure 2, who flew in the unmanned Biosatellite III for 8.8 days in 1969.

It was unfortunate in the extreme that, although the animal functioned quite well for the first several days in orbit, it went into a rapid decline on the 8th day of the flight as judged from the cessation of eating and drinking and a substantial fall in heart rate and blood pressure on that day, all monitored from the ground. The spacecraft was recalled from orbit, and, when the animal was removed from the reentry vehicle, it was in a shock-like state with scarcely perceptible vital signs. Treatment for shock was instituted immediately but, about 12 hr after reentry and despite all therapeutic efforts, ventricular fibrillation developed and the animal died.

The immediate aftermath of this dramatic result was the preliminary and controversial conclusion that weightlessness may have been a primary factor in the failure of the animal subject. However, more careful analysis of the total circumstances surrounding the experiment led to a quite different conclusion (ref. 3).

Prior to the Biosatellite III flight, a total of five flight candidates was actually prepared. On the day before launch, one of the five was selected as the flight animal and the other four were placed in spacecraft mockups to serve as ground controls. All five animals had been prepared some months

before with brain recording electrodes, and, in the 2 weeks just before launch, they received two additional major surgeries, one to implant a special urethral catheter for urine collection and the other to implant four vascular catheters for blood pressure recording. Each of these preparative procedures had been tested individually on monkeys many times before, quite successfully; however, only six monkeys had received all three preparative procedures before the launch period, and success had been marginal at best with these six animals. In the case of the five Biosatellite flight candidates, two of the four ground-control animals died within 3 days of the flight monkey and a third had to be euthanized because of a severely deteriorated physical condition. Thus, only one of the five flight candidates survived the extensive surgical preparations made shortly before the flight, and it may be concluded that it was the sum of these rather than weightlessness that was the primary cause of the demise of Bonny.

In all fairness to the individual experimenters on the Biosatellite III monkey, there was considerable management pressure to maximize the quantity of information return from the flight. And in all fairness to NASA management, the engineering costs associated with the development, construction, launch and recovery of the sophisticated Biosatellite space-flight system were sufficiently large that insistence on making as many measurements as possible on the monkey subject seemed to represent the best approach to cost-effectiveness. In retrospect, it is easy to see that a little less, done well, would have been worth a great deal more than too much, done poorly.

The experience of Biosatellite III also emphasizes the importance of careful and complete experiment validation on the ground before costly orbital payload space is allocated. Long lead-time experiment development funds are just as critically essential to a sound and productive space physiology research program as long lead-time engineering development funds are to a sound and successful space-vehicle program. Optimal management practice would appear to dictate that the intrinsic value of the cargo be at least as great as that of the carrier.

### SCIENTIFIC ATTRIBUTES OF *MACACA NEMESTRINA*

But let us get back to the basic characteristics of *Macaca nemestrina* that qualify it as a prime candidate for space-flight experiments on the effects of weightlessness. According to the most recent taxonomic classification of the Order of Primates by Chiarelli (ref. 4), a subject which is in a constant state of flux, there are currently 180 recognized species. As seen in table 2, adapted from Chiarelli, there are 13 macaques. They are classified as catarrhine, or Old World, primates along with man and the great apes, as opposed to the prosimians and the platyrrhine monkeys of the Americas. The macaques are closely related to the baboons, both genera being part of the same subfamily, Papiinae. In fact, according to Chiarelli (ref. 4), both interspecific and intergeneric hybridization can occur between various species of macaques and baboons. These monkeys have 42 chromosomes, as compared to the 46 for man and 48 for the great apes.

Napier and Napier (ref. 5) give a simple model of the successive grades of organization in primate phylogeny, which is reproduced here as figure 3. It may be seen that the macaques and baboons represent primate species that are in a category second only to the anthropoid apes in their morphological and behavioral similarity to man.

There is one particular basic characteristic of Old World monkeys which, according to Washburn (ref. 6), is never found in New World monkeys, and which has important implications with respect to the use of monkey subjects for research on the physiology of weightlessness. This is the presence of areas of thickened, specialized skin firmly attached to the ischia, which are believed to be an adaptive characteristic of the Cercopithecidae associated with their ability to sit upright for long periods of time. Figure 4 shows the general arrangement of the ischial callosities in five species of Old World monkeys. Ischial callosities are also present in about 36 percent of chimpanzees and occasionally in the gorilla and orangutan, but never in man.

Bernstein (refs. 7 and 8) has made extensive field observations of *Macaca nemestrina* in Malaya, and describes it as primarily an arboreal animal spending the largest portion of the daylight hours at medium levels of the forest, but descending periodically to the ground to feed and travel to water. Washburn (ref. 6) describes the baboon in much the same way, and adds the observation that sometimes these animals nap for short periods, both sitting and lying on the ground as well. He goes further to generalize that the ischial callosities of Old World monkeys not only make it possible for these animals to spend most of the day sitting on tree branches, but also to sleep in the sitting position on branches during the night, which they habitually do. These monkeys, then, must be regarded as being primarily a sitting animal, more so probably than even the anthropoid apes and man.

From the point of view of space physiology experimentation, this attribute makes long-term seated restraint an entirely feasible and well-tolerated condition. This is particularly true of *Macaca nemestrina* with its exceptionally calm and patient disposition, as we have already considered.

There is an even more important advantage to using these habitually-sitting primates as subjects for research on the physiological effects of weightlessness, and that is the fact that such animals have evolved with the Earth-gravity vector directed along the long axis of the body, or  $+G_z$  direction, as has man. According to Napier and Napier (ref. 5), supporting evidence for truncal erectness as a characteristic of primates is found in the fact that the foramen magnum of the typical mammalian skull is directed posteriorly, while that of primates is directed inferiorly. This  $90^\circ$  ventral migration of the foramen magnum in the course of primate evolution must be regarded at least partly as an adaptation to the vertical posture of the trunk in primates.

It is well known that man displays specialized reflex responses which bring about complex cardiovascular adjustments when he alternates between horizontal and vertical body positions. It now appears that after man remains continuously recumbent or weightless for several days or more, his cardiovascular responses to  $+G_z$  are significantly altered, and that this is one of the major physiological changes produced by weightlessness. Thus, there is a strong rationale for using basically vertical animals like most nonhuman primates rather than basically horizontal animals like most other mammals as surrogates for man in this kind of research. Indeed, as shown in the earlier paper in this Symposium from our laboratory (ref. 9), *Macaca nemestrina* responds to prolonged recumbency in much the same way as does man.

Another important consideration in the selection of an appropriate animal model is the matter of body size or mass. It is evident from Galileo's Principle of Similitude that the larger the animal, the greater is the influence of gravity in determining form and function. This basic biological principle was recognized many years ago by D'Arcy Thompson (ref. 10), who pointed out as an example the increase in fraction of the total body mass represented by the skeleton as animals get

larger: from 7 percent in the mouse and rat through 14 percent in man to 25 percent in the elephant. It has also been theorized by Smith (ref. 11) that there is probably a minimum threshold body size, below which gravitational force is no longer significant in determining form and function. He places this threshold size at about 20 g.

In the scale of terrestrial mammals from mouse to elephant, we are dealing with somewhat better than five orders of magnitude in body mass, with man about midway logarithmically. Thus, in selecting a surrogate for man to study the physiological effects of the removal of the influence of gravity, as occurs in space flight, it would appear most appropriate to select an animal species with an adult body mass within one order of magnitude of that of man; i.e., of at least 7 kg. *Macaca mulatta* with a mature body mass of 11 kg, *Macaca nemestrina* with 14.5 kg, and *Papio anubis* with 30 kg (ref. 12), all fulfill this basic requirement.

Metabolically, there is little to choose among the larger monkeys, because they are mostly omnivorous like man. Two major exceptions are the colobine monkeys and the gorilla, which are strict vegetarians in nature (ref. 5). However, as mentioned by Bernstein (ref. 8), *Macaca nemestrina* kept in captivity in Malaya subsist well on kitchen scraps, and experiments in our laboratory (refs. 13 and 14) have shown that this species thrives on a diet balanced according to human dietary standards.

On a much more subtle level, Haffleigh and Williams (ref. 15) have measured the degree of similarity between the plasma albumins of various primate species and human albumin by immunologic titration against a human antiserum. Their results, summarized in table 3, show that only the chimpanzee and gorilla albumins resemble human albumin more closely than does macaque albumin. Numerous other serological reactions have been used to examine the immunological distance between man and other animals, and the close sequence of man, chimpanzee, gorilla, macaque, and baboon is almost invariably the same. As a matter of side interest, based on this immunological similarity among the primates, as early as 1910, Unger (ref. 16) attempted transplantation of kidneys from a *Macaca nemestrina* to a human patient with renal disease in what may have been the first of the organ transplant operations in man.

An exhaustive review of the scientific literature on *Macaca nemestrina* is beyond the scope of the present paper. Suffice it to say that it is a large literature, which is growing steadily as the merits of this species as an experimental animal become better known. At present, the general availability from commercial animal trappers of *Macaca mulatta* to experimenters in this country has been readier than that of *Macaca nemestrina*. However, it is well established that *Macaca nemestrina* breeds prolifically in captivity, and in fact in our own laboratory we have shown that this species breeds equally well the year around (ref. 17). Therefore, as the feral pools of all species of experimental primates continue to shrink, it will be entirely feasible to provide quantities of pig-tailed monkeys from breeding colonies similar to the large *Macaca nemestrina* colony being operated by the Regional Primate Research Center of the University of Washington.

## SUMMARY

We conclude by reiterating the advantages of close phylogenetic relationship and closely comparable body size to man of the Old World primates as surrogates in physiological research. We

reiterate the advantages of the more practical general management and handling of the Cercopithecoid family of monkeys, as compared to the great apes, in the demanding orbiting spacecraft environment. We reiterate the advantage of a short tail and the presence of ischial callosities in these monkeys, which permit them to remain in comfortable seated restraint for long-duration experiments. Finally, among the Cercopithecoids, we emphasize the singularly calm, quiet, and patient temperament of *Macaca nemestrina* as compared to other species. All of these considerations lead to the conclusion that the pig-tailed monkey is an optimal choice as a flight candidate to investigate many of the problems of space physiology.

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TABLE 1.— COMPARATIVE SUITABILITY OF THREE SPECIES OF MACAQUES  
FOR SPACE-FLIGHT PHYSIOLOGICAL EXPERIMENTATION

Criterion	<i>Macaca nemestrina</i>	<i>Macaca mulatta</i>	<i>Macaca speciosa</i>
Adult body size	B	C	C
Temperament	A	C	C
Trainability	A	C	C
Absence of vocalization	A	C	C
Manual skill	B	C	C
Seated restraint	A	B	B
Supine restraint	A	--	--
Handling	B	C	C
Breeding in captivity	A	B	--
Surgical tolerance	B	B	--
Availability	C	A	D
Physiological base-line data	B	C	D
Other base-line data	C	B	D
Space-flight experience	B	C	--
Grade-Point Average	3.29	2.46	1.80

A = 4.0 grade points

B = 3.0 grade points

C = 2.0 grade points

D = 1.0 grade points

F = 0.0 grade points

TABLE 2.— TAXONOMIC CLASSIFICATION OF THE 180 LIVING PRIMATE SPECIES  
ACCORDING TO CHIARELLI (REF. 4)

Suborder	Infraorder	Superfamily	Family	Subfamily	Genera	No. of species				
PROSIMII (44 sp.)	Tupainformes	Tupaioidea	Tupaiidae	{ Tupainae Ptilocercinae	{ <i>Tupaia</i> <i>Dendrogale</i> <i>Urogate</i> <i>Ptilocercus</i> <i>Loris</i> <i>Nycticebus</i> <i>Arctocebus</i> <i>Perodicticus</i> <i>Galago</i> <i>Lemur</i> <i>Hapalemur</i> <i>Lepilemur</i> <i>Cheirogaleus</i> <i>Microcebus</i> <i>Phaner</i> <i>Indri</i> <i>Avahi</i> <i>Propithecus</i> <i>Daubentonia</i> <i>Tarsius</i>	9 2 1 1 1 2 1 1 5 5 2 1 2 2 1 1 2 1 3				
					Lorisiformes	Lorisoidea	{ Lorisidae Galagidae			
	Lemuriformes	Lemuroidea	Lemuridae	{ Lemurinae Cheirogaleinae						
					Tarsiiformes	Tarsioidea	Daubentoniidae Tarsiidae			
	ANTHROPOIDEA (136 sp.)	Platyrrhini (51 sp.) (New World)	Callithricoidea	Callithricidae	{ Callithricinae Callimiconinae	{ <i>Callithrix</i> <i>Leontideus</i> <i>Cebuella</i> <i>Saguinus</i> <i>Callimico</i> <i>Aotes</i> <i>Brachyteles</i> <i>Callicebus</i> <i>Pithecia</i> <i>Chiropotes</i> <i>Cacajao</i> <i>Alouatta</i> <i>Saimiri</i> <i>Cebus</i> <i>Ateles</i> <i>Lagothrix</i>	3 3 1 14 1 1 1 3 2 2 3 5 2 4 4 2			
						{ Aotinae Pitheciniae Alouattinae Cebinae Atelinae				
					Ceboidea		Cebidae			
			Catarrhini (85 sp.) (Old World)	Cercopithecoidea	Cercopithecidae	{ Papiinae Cercopithecinae	{ <i>Macaca</i> <i>Papio</i> <i>Cercocebus</i> <i>Theropithecus</i> <i>Cercopithecus</i> <i>Erythrocebus</i> <i>Presbytis</i> <i>Pygathrix</i> <i>Rhinopithecus</i> <i>Simias</i> <i>Nasalis</i> <i>Colobus</i> <i>Hylobates</i> <i>Symphalangus</i> <i>Pongo</i> <i>Pan</i> <i>Gorilla</i> <i>Homo</i>	13 7 5 1 22 1 14 1 2 1 1 5 6 1 1 1 1		
Colobidae							Colobinae			
						Hylobatidae				
								Pongidae		
									Hominidae	



TABLE 3.— IMMUNOLOGICAL RESEMBLANCE OF THE ALBUMIN OF VARIOUS MAMMALIAN SPECIES TO HUMAN ALBUMIN. DATA FROM HAFLEIGH AND WILLIAMS (REF. 15)

Order	Family	Genus	Similarity in percent
Primates	Hominidae	<i>Homo</i>	100
	Pongidae	<i>Pan</i>	97
		<i>Gorilla</i>	92
	Hylobatidae	<i>Hylobates</i>	79
	Cercopithecidae	<i>Macaca</i>	82
		<i>Papio</i>	79
		<i>Cercocebus</i>	79
		<i>Cercopithecus</i>	79
		<i>Erythrocebus</i>	72
	Colobidae	<i>Colobus</i>	80
	Cebidae	<i>Aotes</i>	74
		<i>Lagothrix</i>	61
		<i>Saimiri</i>	60
		<i>Ateles</i>	58
		<i>Cebus</i>	45
	Callithricidae	<i>Saguinus</i>	54
	Lemuridae	<i>Lemur</i>	37
	Indriidae	<i>Propithecus</i>	22
	Lorisidae	<i>Perodicticus</i>	31
Artiodactyla	Galagidae	<i>Galago</i>	28
	Tupaïidae	<i>Tupaia</i>	31
Rodentia	Suidae	<i>Sus</i>	8
	Erethizontidae	<i>Erethizon</i>	17

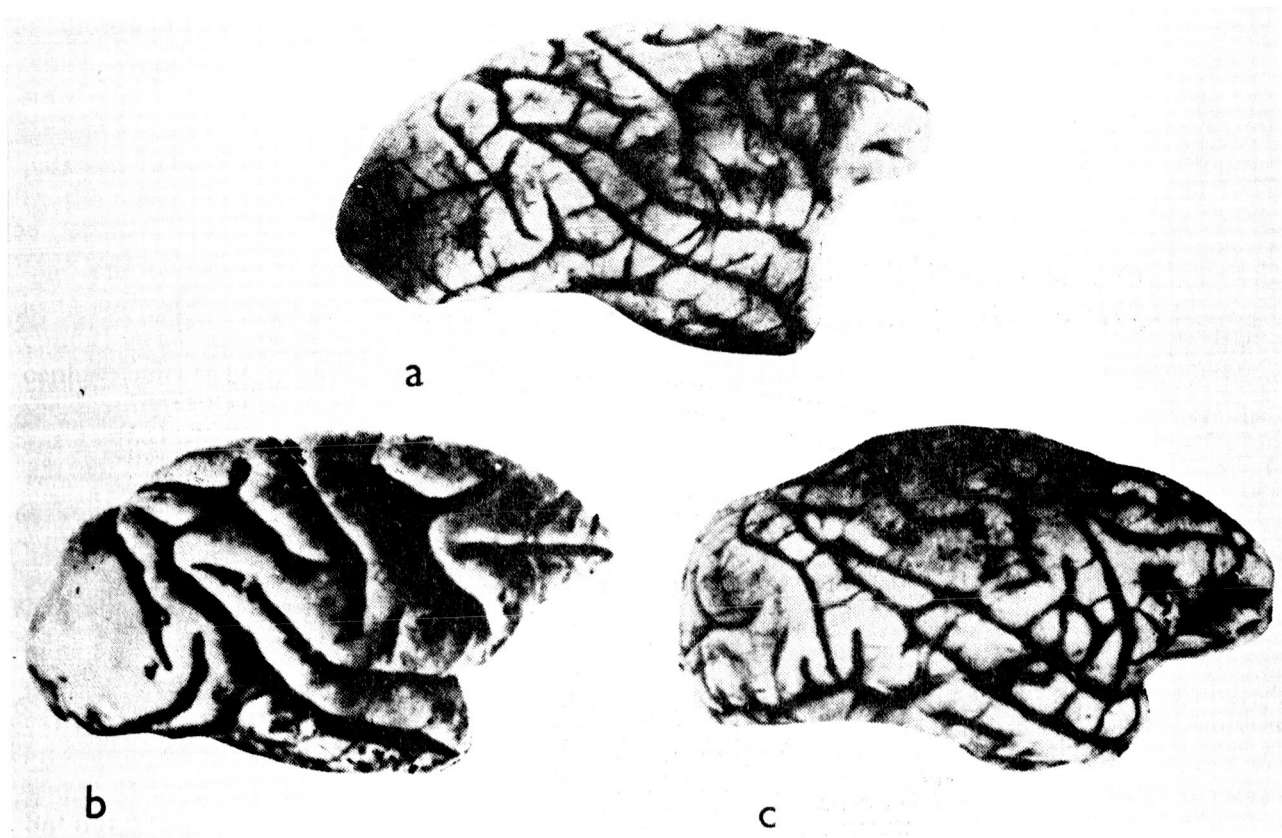
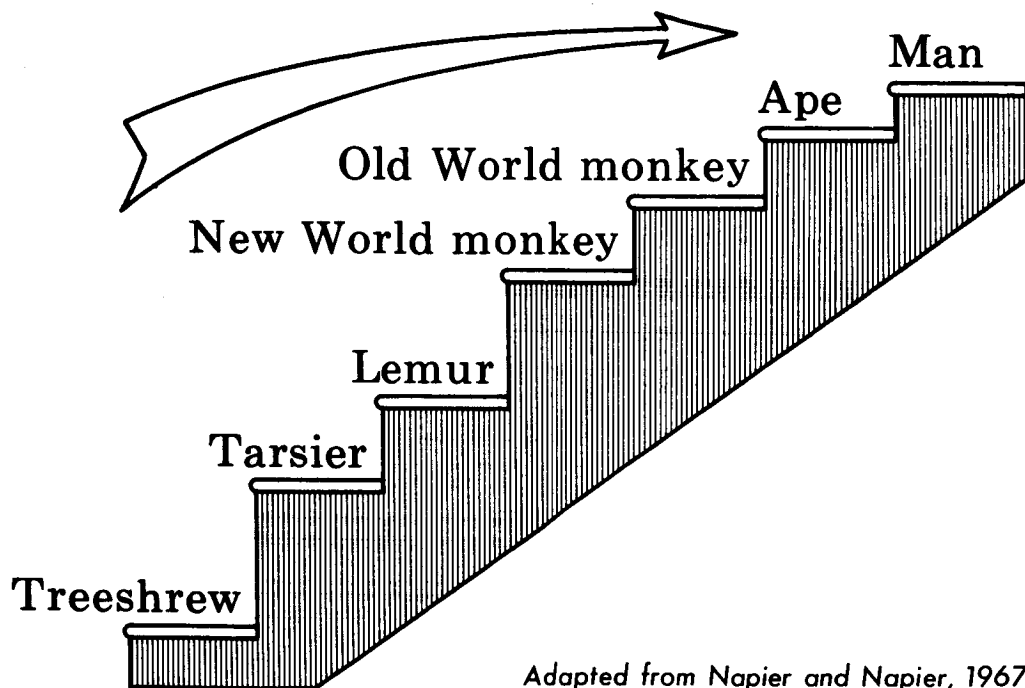


Figure 1.— The brain, cerebellum removed, of (a) *Macaca nemestrina*, (b) *Macaca mulatta*, (c) *Papio anubis*. Reproduced from Cole (ref. 2) with permission from the author and The Zoological Society of London.



Figure 2.— Bonny, the *Macaca nemestrina* of NASA Biosatellite III.

INCREASING COMPLEXITY OF  
STRUCTURAL AND BEHAVIORAL ORGANIZATION



Adapted from Napier and Napier, 1967

Figure 3.— Successive morphological and behavioral grades found among living primates. The height of each step indicates the degree of difference between each grade. *Macaca nemestrina* is an Old World monkey.

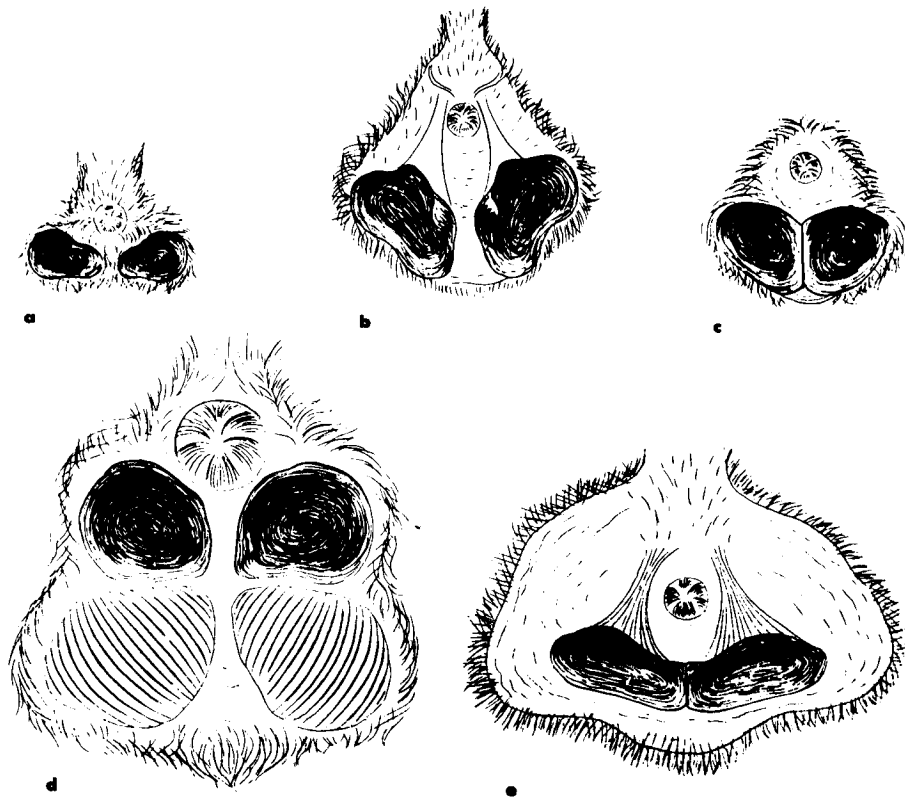


Figure 4.— Perianal region, showing the ischial callosities, of five primates: (a) *Cercopithecus mona*, (b) *Macaca nemestrina*, (c) *Macaca sylvana*, (d) *Theropithecus gelada*, (e) *Papio papio*. Reproduced from Napier and Napier (ref. 5) with permission of the authors and Academic Press Inc. (London) Ltd.

## CONSIDERATION OF OTHER PRIMATE SPECIES AS FLIGHT ANIMALS

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Several primate species have been discussed during the last two days, and some of them have attributes which would make them satisfactory flight animals. These animals have had a lot of time and energy invested in them by investigators, and a good deal of base-line information has been collected about them. It would serve no good purpose, therefore, to pick a species such as the rhesus monkey and identify it as the sole flight animal. For those who have not worked with other primate species and do not have a good collection of data concerning them, the rhesus would be the animal of choice because of the enormous amount of data which have been accumulated about it. Furthermore, the species of animal that is flown will be dependent to some extent upon the nature of the subject to be studied. A very small primate might, for example, be undesirable for some types of cardiovascular investigation.

In this paper a brief survey is given of the different types of primates which might be used as flight animals, and the pros and cons of using them are discussed.

The discussion below gives the general relationship between the primate groups.

Some lemurs, which are pro-primates, could be used for flight experiments, but they are endangered animals restricted to Madagascar, and it would be impossible to obtain permission to export them from Madagascar; in any case, it would be unethical to do so. Other possibilities include the New World monkeys and many species of African and Asiatic monkeys.

Since flight experiments with primates are planned because of their close relationship to man, it would make sense to use those primates which showed the closest relationship to man. Obviously, the anthropoid apes such as the chimpanzee (*Pan troglodytes*), the orangutan (*Pongo pygmaeus*), and the gorilla (*Gorilla gorilla*) would, in theory, be the best flight animals on this basis. Young chimpanzees could be used for certain experimental procedures, especially if they were restrained, but in an unrestrained condition they are very destructive. Gorillas and orangutans, while not as destructive as chimpanzees, are immensely strong and they are also endangered species, so they should be excluded from further consideration.

Both Dr. Stone and Dr. Pace have referred to the importance of flying a vertical animal, that is, one which more nearly approaches the erect posture. This is an important point and should be used, as Dr. Simmonds has mentioned, in making a decision as to whether we should fly primates at all but instead turn our attention to a quadruped such as a rabbit or a dog. In the development of the erect posture, there were not only very profound anatomical changes but also physiological changes, especially of a hydrodynamic nature, which had to take place. It became essential for large, strong, leg muscles to develop to maintain physically the erect posture and also to support the large leg veins and prevent blood from pooling in them. So the best animal model in which to study weightlessness would be one which is truly vertical and walks bipedally. There are no nonhuman primates which do just that. There are, however, some which locomote in a vertical position; none of these has the muscular legs and large leg veins characteristic of man and in which blood could

pool after a prolonged period of weightlessness or bedrest. The gibbon brachiates in a vertical position by the use of its large arms. It has small and relatively insignificant legs. The spider monkey (fig. 1) of South America fits into the same category. Another is the spectral tarsier (*Tarsius spectrum*, fig. 2) which progresses in a saltatory fashion on its two legs; however, its legs are thin and bony and it, too, is not a good model for man.

Since these vertical animals are not really suitable models, it is necessary to consider the other nonhuman primates as flight animals using a variety of criteria for making a judgment.

The tree shrews (*Tupaia*, fig. 3) are insectivores, and there is some controversy as to whether they truly belong to the primates. They are quadrupedal, and apart from sitting up from time to time, they are very much horizontal animals. From this point of view, there would be no advantage in using them as flight animals over, say, rats or rabbits.

The New World monkeys include the marmosets (fig. 4), the tamarins, and the pinchés (fig. 5), as well as squirrel monkeys, capuchins, howlers, and others. There is considerable base-line information about some of the tamarins (fig. 6). They progress in a quadrupedal fashion though they tend to sit up on their tails when at rest. They represent the simplest of primates, and some of them might be suitable for flight experiments if weight were a serious consideration. The same applies to the pygmy marmoset (*Cebuella*, fig. 7), which is the smallest of the true primates. However, most countries in South America have banned the export of primates, and none of them are now easy to obtain. The most monkey-like of the more primitive South American primates is the squirrel monkey (*Saimiri sciureus*, fig. 8). The squirrel monkey travels by climbing in the trees using its arms and legs and its tail as a balancer. Another group of South American monkeys is represented by the Cebidae. This includes the capuchins, woolies, spider monkeys, and the howlers. They all have a fifth holding appendage in the form of a prehensile tail. The value of the capuchin as a flight animal has been discussed in detail by Dr. Winget. It is a very intelligent animal and has much to recommend it. The long prehensile tails of all these animals, however, introduce complications when they are considered as models for man in weightlessness studies. They may be suitable, however, for some types of experiments.

Let us turn to the Old World monkeys. The biggest group of these is the Cercopithecoidea; they include the Swamp monkeys, the talapoints (fig. 9), the guenons, and the red or military monkeys. The Swamp monkeys can be eliminated straight away since there is no base-line information on them and they are difficult to obtain. The talapoin monkey is really a dwarf guenon, it is a small (10 in. in height), generalized type of animal and weighs no more than a squirrel monkey. It rests in a vertical position and would be an excellent monkey for space research. The main drawbacks in the use of those animals would be that they are not readily available at this time, although they are plentiful in the wild, and there is very little base-line information concerning them.

The guenons represent one of the largest groups of monkeys and they are small and plentiful. There are at least 100 different types of guenons, and some are very exotic in appearance. They were very well known to the Mediterranean people before the birth of Christ; in fact, they were probably the first monkeys to be known to the people in that part of the world.

Probably the biggest groups of guenons are the vervets or green monkeys (fig. 10). Green monkeys are the most commonly imported of all guenons. They are hearty, and sudden changes in

temperature do not worry them much. They have been able to acclimatize themselves to the stiffer conditions of the northern latitudes much better than most other species of monkeys. The green monkey is an aggressive and bold animal. The Sykes monkey (fig. 11) is about the same size and is tameable and easy to handle.

The Mona monkey is a guenon having a habitat which extends right across Africa. It is a playful animal, but seems to get angry easily and can be very aggressive.

The Diana monkey is a guenon that is very elegant in appearance and sometimes reaches 2 ft in height. Other guenons include the mustached monkeys (fig. 12), the white-nosed monkeys, and the DeBrazza monkeys. All guenons are very social animals and live usually in large groups, but they may occur in smaller and even family-sized groups. When they are young, guenons can be easily tamed, but when they get older, they are unpredictable and can inflict dangerous bites. They eat a wide range of foodstuffs in the wild – fruits, leaves, shoots, nuts, insects, wild honey, young birds, and birds' eggs.

Amongst the guenons there are many which would be excellent flight animals from the point of view of size and ease of handling, but the two main drawbacks are that they are not easily available and there is practically no base-line data about any of them with the exception of, in some cases, behavioral observations.

The red monkeys or Patas monkeys (fig. 13) live mainly in the west part of Africa. They are as quadrupedal as a dog and are high-speed runners, having been described as "primate cheetahs." They are very much ground living animals. The young will sometimes run a short distance in an erect bipedal fashion, and when an adult is running away from trouble, it will sometimes rise briefly into an upright position and run bipedally for a few steps while it looks back over its shoulder; then it will hop back into a four-legged gallop. There is no special reason to select the Patas monkey as a flight animal. There is limited basic information about it, its physical behavior, i.e., the way it runs and sits, is very dog-like and it is a fairly big animal.

The genus *Macaca* includes quite a number of monkeys, among those are the rhesus; the Barbary Ape; the bonnet; the toque monkey; the lion-tailed macaque, which is approaching extinction and is on the endangered list; the pig-tailed macaque (fig. 14), and the crab-eating or Java monkey. There are also the Assamese macaque, the Formosan rock macaque, the stump-tailed macaque (fig. 15), the Moor macaque, and the Celebes black ape. The last two live only on the Celebes Islands north of Australia, and most of the others range from the Celebes through all of Southeast Asia, the Philippines, Borneo, Java, and Sumatra into India and Ceylon (Sri Lanka) and to the east and north to parts of Afghanistan, Tibet, China, Japan, and Formosa. Their habitat ranges from sea level to as much as 13,000 ft and varies from tropical rain forests to mangrove swamps and grassland. All macaques seem to be able to swim. The Formosan macaque lives on beaches and eats shellfish.

The rhesus macaque (*Macaca mulatta*) is probably the best known of all macaques. It is a fairly large and strong monkey, and the large males can reach a weight of over 30 lb. It is highly intelligent and aggressive. Its value as a flight animal is described elsewhere in this volume.

Japanese macaques (*Macaca fuscata*) are reasonably plentiful, and there is a good deal of information concerning them. However, they are much more limited in numbers than the rhesus

monkey and are so close to the rhesus in size and structure, general behavior, and pathology that there would be no special reason for using them. Some of the more exotic types of macaques such as the toque monkey, the lion-tailed macaque, and the Formosan macaque are too rare to be used for experimental studies in space.

Probably the most suitable of the macaques, apart from the rhesus, for space studies are the pig-tailed monkey (*Macaca nemestrina*) and the Java monkey (*Macaca fascicularis*). Both of these are plentiful in the wild, and the Java monkey may well be the most plentiful of all monkeys, ranging as it does all over Southeast Asia.

Extensive base-line data have been accumulated by Dr. Nello Pace on the pig-tailed macaque, and there is no doubt that this would be a good flight animal. The Java macaque would also be a good animal for this purpose. It is smaller than either the rhesus or the pig-tailed animals and is well motivated and hardy, but there is not at present as much base-line data about it as for the rhesus. Behaviorally, it has been very much less studied.

Consideration should also be given to other Old World monkeys such as the mangabeys, baboons, drills, and mandrills.

Mangabeys (fig. 16) are rather large animals and the body length may reach 36 in. They have a rather generalized or primitive structure and are probably close to the ancestral animals from which the drills, mandrills, and baboons developed. They are forest living animals. In captivity they are very agreeable and learn to respond well to handling. There is little base-line information and since they are large and strong, they are not recommended as flight animals.

In Asia, Africa, and Europe, early man seems to have come in contact with baboons (fig. 17), since they figure extensively in his paintings and drawings. This was especially so in Egypt where the baboon was worshipped. Also, in that country it was supposed to have been trained for many roles as a fisherman, a servant, and in some cases, as a helper in the field. It was also supposed to serve wine at coronations and was used as an entertainer.

This historical information suggests that baboons are very tractable animals, but in fact they are big and powerful. The baboon progresses quadrupedally and is built rather like a dog. It has a dog-like face and a dog-like body, but with longer arms than legs so that its body slopes backwards when it walks. The baboon has been used in a number of laboratories for cardiovascular studies, and the Southwest Foundation for Research has accumulated an enormous amount of base-line data concerning them. Since they live on the ground, they are not as good for some types of space research as some other nonhuman primates that are climbers and spend much more time in a vertical or semivertical position. Also, they are very heavy animals, and this would not favor their use as flight animals.

The drills and mandrills are also too big and strong for space studies, and there is again very little base-line information concerning them.

The use of the chimpanzee as a flight animal has been discussed elsewhere in this volume. The other great apes, the orangutan and the gorilla, are endangered animals and are too strong to be considered for space experimentation.



In summary, while there are many species of monkeys that can be considered as possible flight candidates, various factors suggest that the most desirable animals for space studies are the rhesus monkey, the pig-tailed monkey, the Java monkey, and the squirrel monkey. The capuchin monkey has some assets for certain types of space experimentation as is explained in another article in this volume.



Figure 1.— Spider monkey (*Ateles*).



Figure 2.— Spectral tarsier (*Tarsius spectrum*). (By permission of the late Sir Wilfrid Le Gros Clark.)

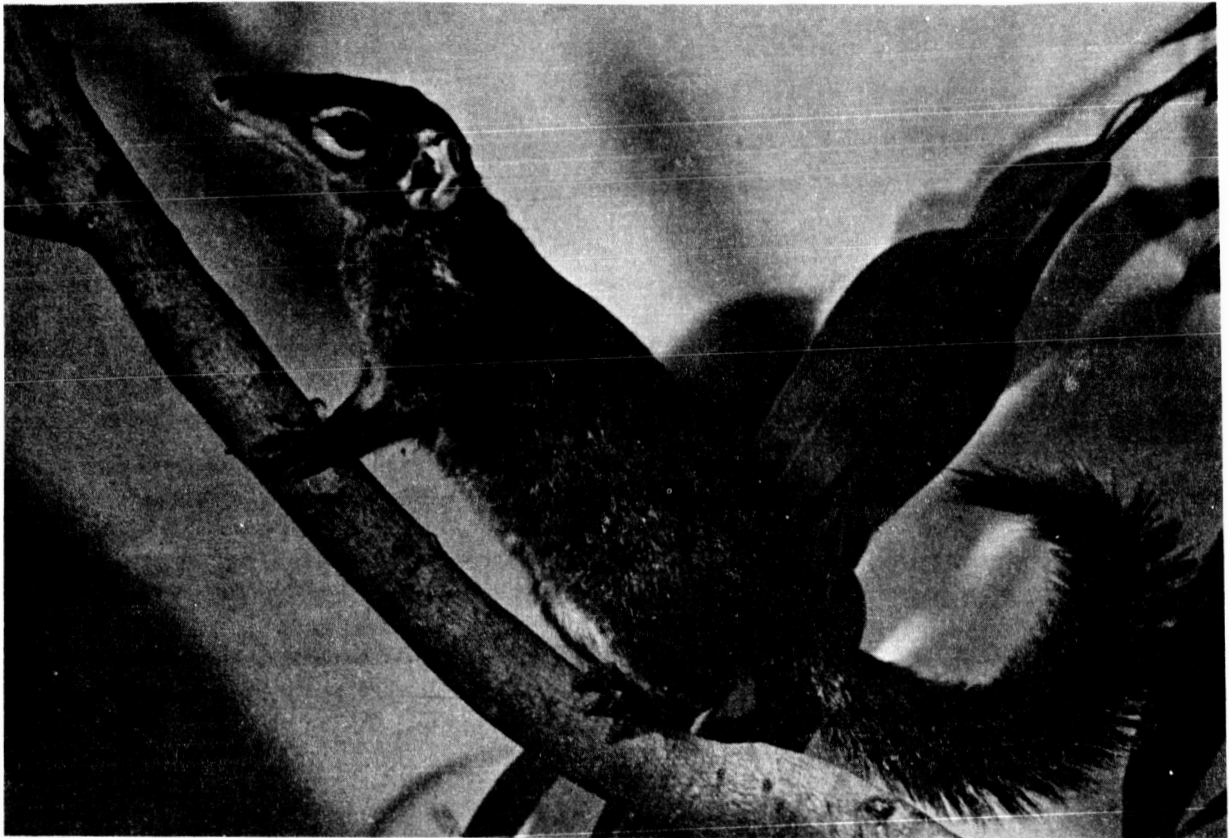


Figure 3.— Tree shrew (*Tupaia*). (Courtesy of San Diego Zoo.)

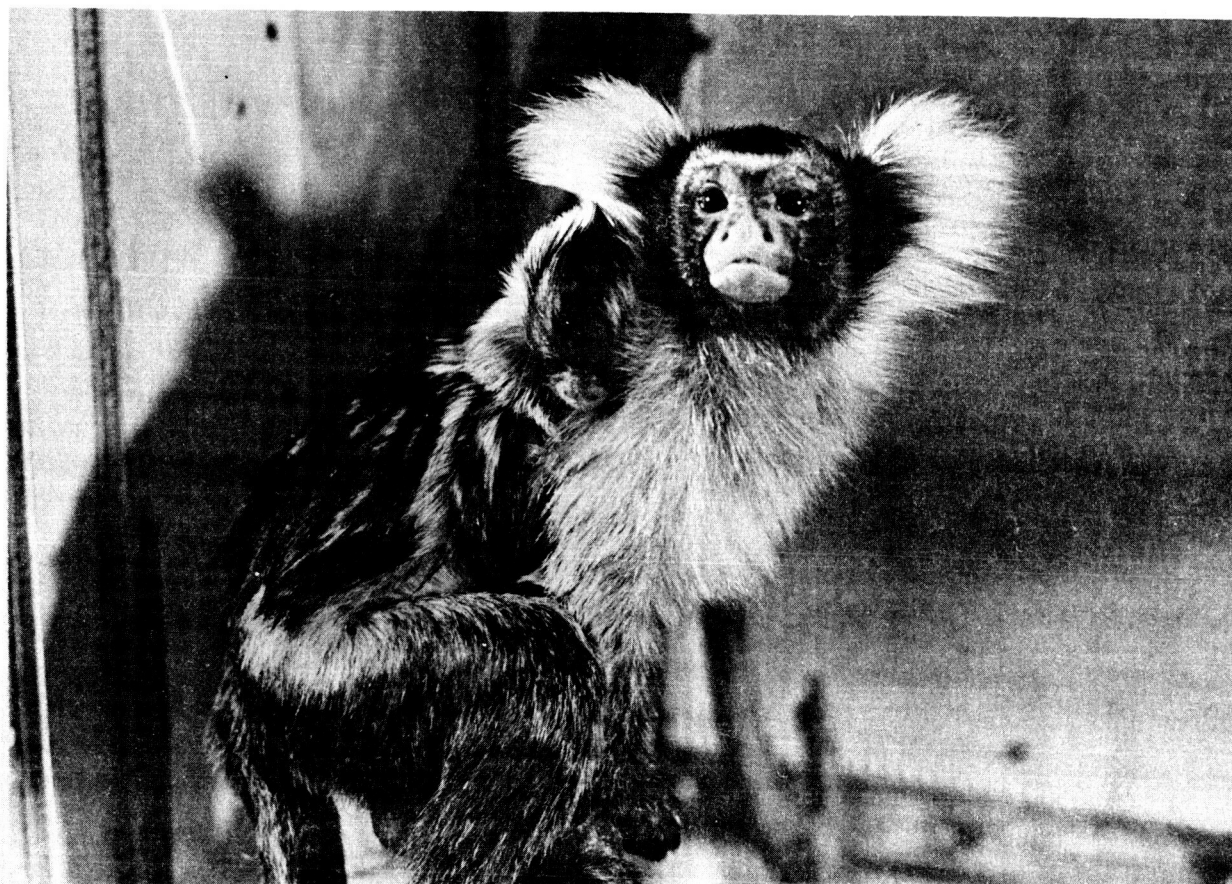


Figure 4.— White-eared marmoset (*Callithrix aurita*). (Courtesy of Mr. Frank Dumond.)



Figure 5.— Cottontop pinche (*Saguinus oedipus*). (Courtesy of Mr. Frank Dumond.)



Figure 6.— Moustached tamarin (*Saguinus mystax*). (Courtesy of Mr. Frank Dumond.)





Figure 7.— Pygmy marmosets (*Cebulla pygmaea*). (Courtesy of San Diego Zoo.)





Figure 8.— Squirrel monkey (*Saimiri sciureus*). (Courtesy of Mr. Frank Dumond.)



Figure 9.-- Talapoin monkey and young (*Miopithecus talapoin*).



Figure 10.— Green monkey (*Cercopithecus aethiops*), Grivet. (Courtesy of Cheyenne Mountain Park Zoo.)



Figure 11.— Sykes monkey (*Cercopithecus albogularis*).

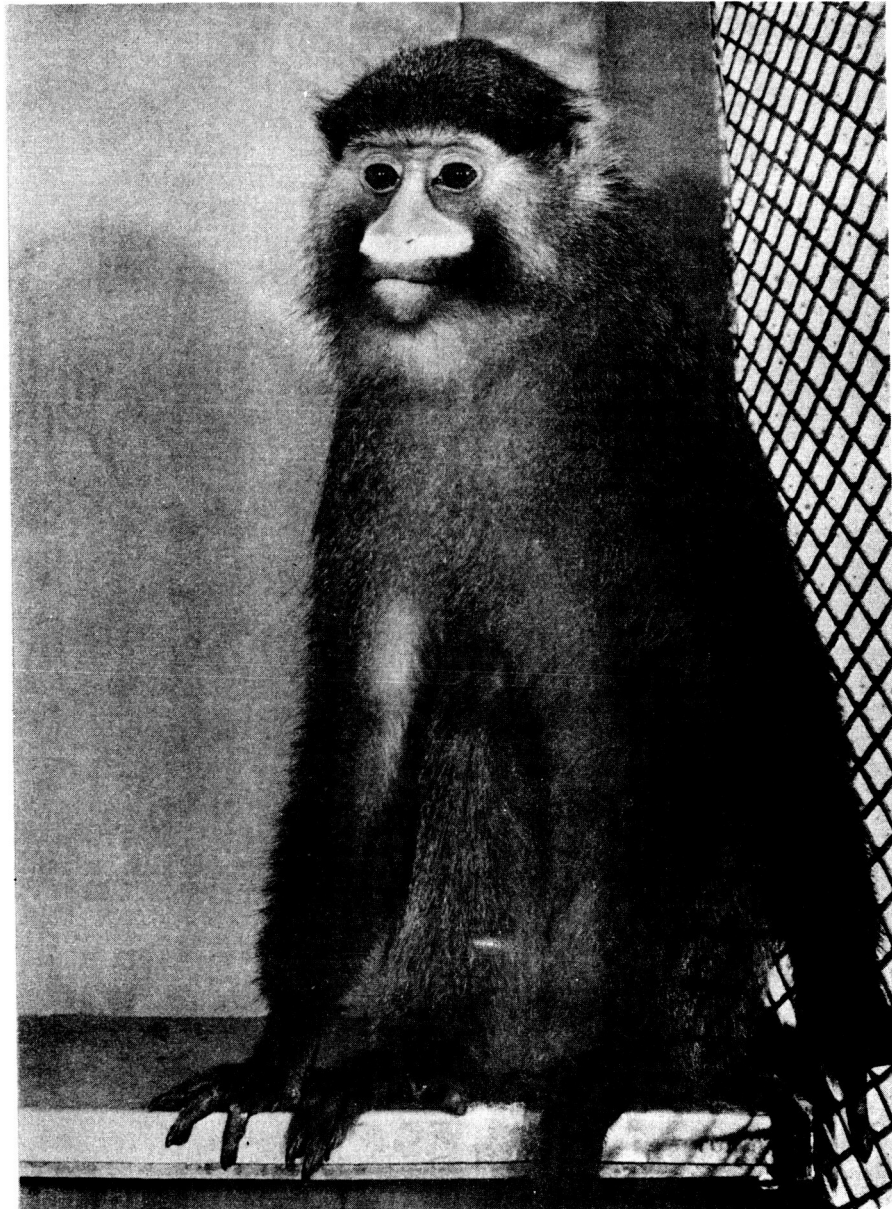


Figure 12.— Moustache guenon (*Cercopithecus cephus*).

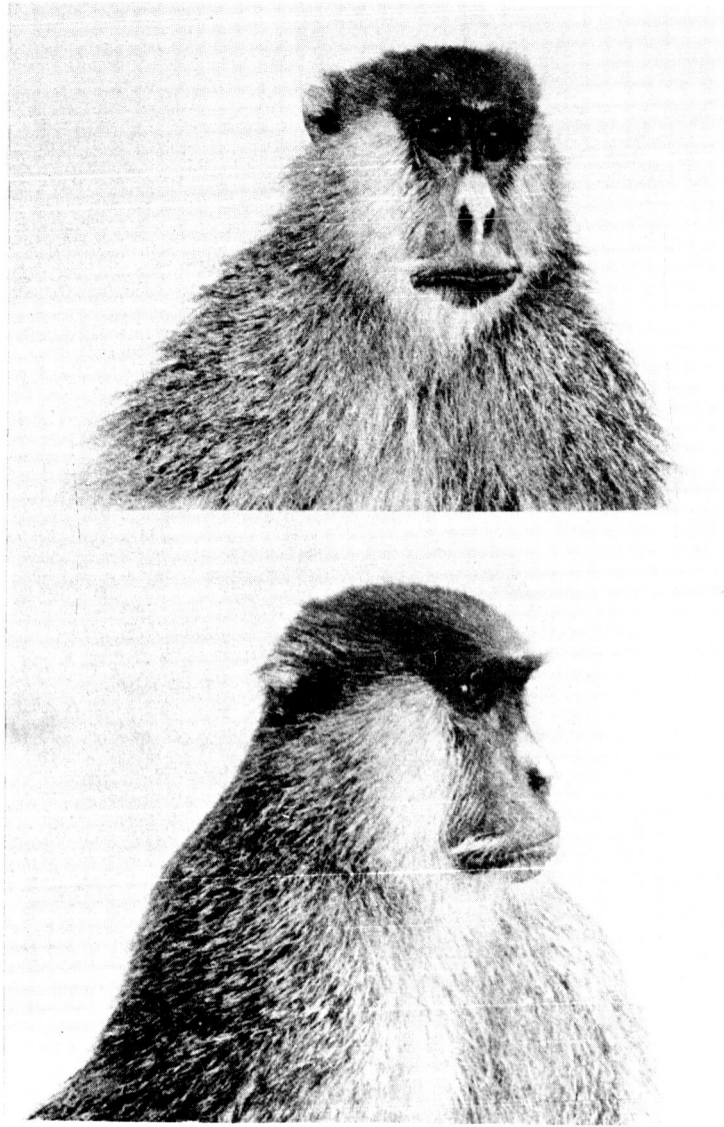


Figure 13.— Patas monkey (*Erythrocebus patas*). (Courtesy of Bull. Amer. Mus. Nat. Hist.)





Figure 14.— Pig-tailed macaque (*Macaca nemestrina*).

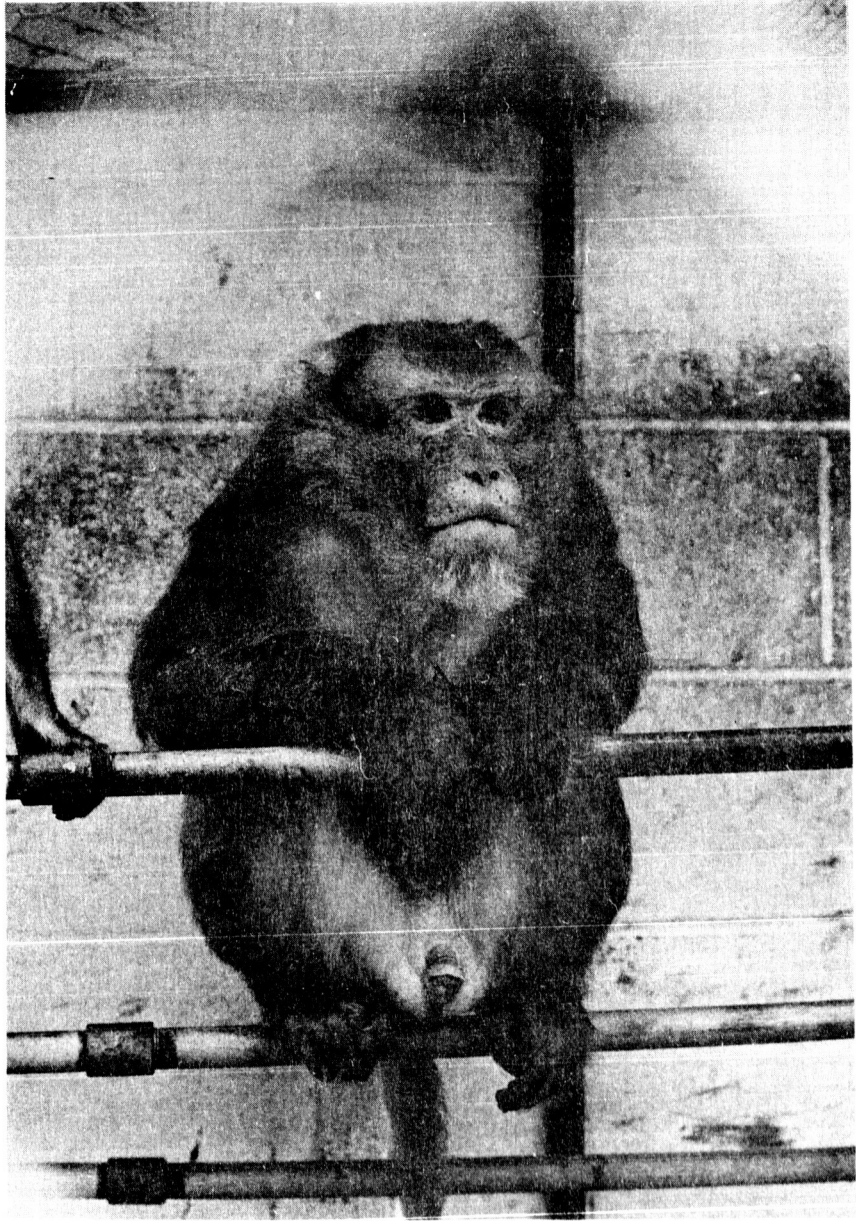


Figure 15.— Red stump-tailed macaque (*Macaca speciosa*).





Figure 16.— Crested mangabey (*Cercocebus aterrimus*). (Courtesy of the Cheyenne Mountain Park Zoo.)

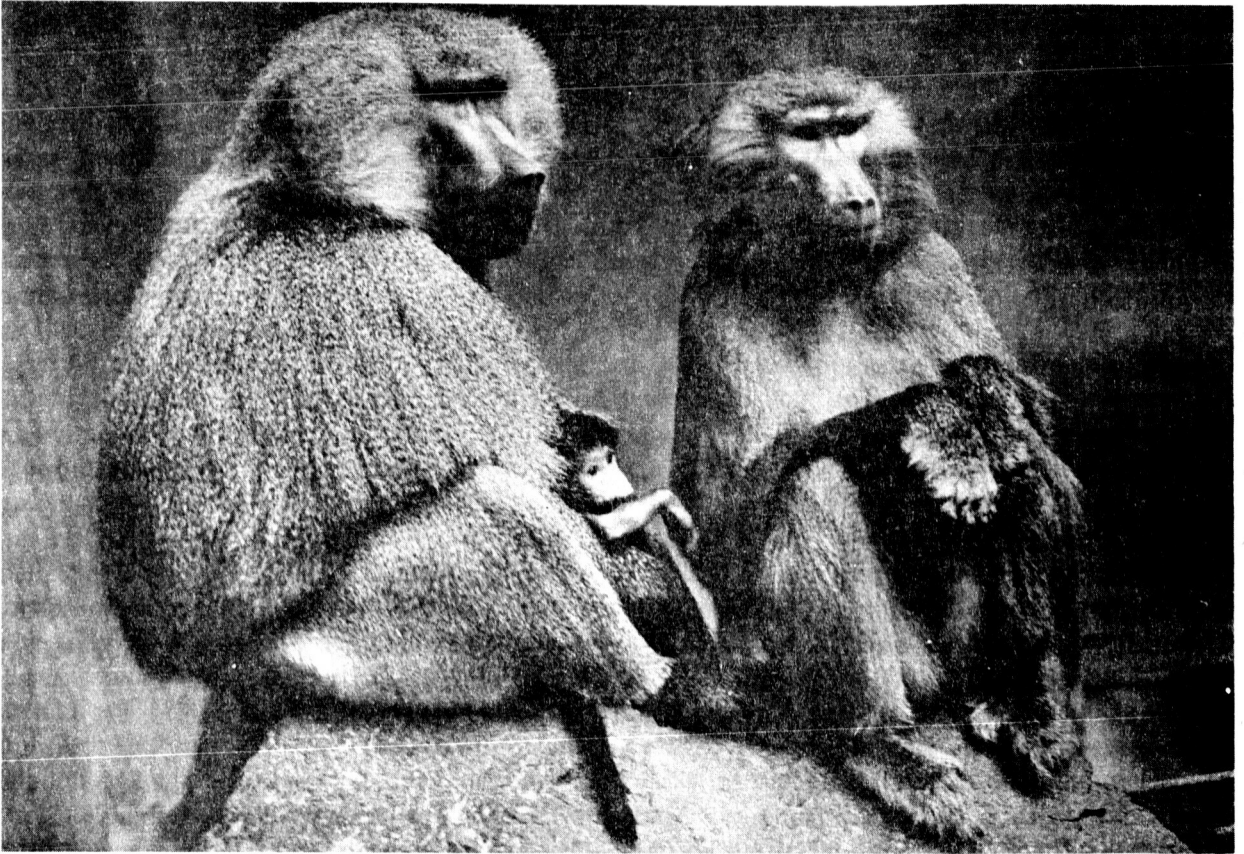


Figure 17.— Hamadryad baboon family (*Papio hamadryas*). (Courtesy of San Diego Zoo.)

# THE RHESUS (*Macaca mulatta*) AND CRAB-EATING (*Macaca fascicularis*) MONKEYS

## IN CARDIOVASCULAR AND AEROSPACE RESEARCH

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### INTRODUCTION

The research reported in this paper was conducted by personnel of the Biodynamics Branch, Environmental Sciences Division, USAF School of Aerospace Medicine, Aerospace Medical Division, AFSC, United States Air Force, Brooks AFB, Texas, and the Anesthesia and Operating Service, Brooke Army Medical Center, Fort Sam Houston, Texas. It was supported in part by NASA Contract A-94544.

The animals involved in this study were maintained and used in accordance with the Animal Welfare Act of 1970 and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences – National Research Council.

Man encounters many stressors in the environment of advanced aircraft and aerospace systems which may affect mission performance. Design and development of new high-performance fighter-attack aircraft such as the F-15 and air-combat fighter (F-16) require continuous and optimal crew performance in the operational environment.

A primary objective at the USAF School of Aerospace Medicine has been to determine the effects of acceleration and other environmental stressors on pilot physiologic performance (refs. 1 and 2). Special emphasis has been placed on the cardiovascular responses to acceleration stress (refs. 3 and 4), definition of cardiovascular endpoints and safe exposure limits in a high-G air-combat maneuvering environment, and the influence of new methods which can increase tolerance of the cardiovascular system to acceleration stress (ref. 1). A correlation between direct and indirect endpoints to G stress, measured in experimental animals and man, is very important in this research.

Animal models have been used (i) to investigate the effects of gravito-inertial forces on pilot incapacitation and performance impairment, (ii) to define human physiologic tolerance and safe exposure limits to these environments, and (iii) to obtain data which can be used to evolve new methods to improve man's G tolerance to match the structural capability of new generation aircraft. Two nonhuman primate species, the *Macaca fascicularis* (crab-eating monkey) and *Macaca mulatta* (rhesus monkey), have been used in our research. The *Macaca fascicularis* has been used to study the effects of environmental stress and atherosclerosis on cerebral blood flow and function (ref. 5). The *Macaca mulatta* has been used to study the effects of acceleration stress (ref. 6) and anesthetic agents (ref. 7) on myocardial and cardiovascular function.

## ENVIRONMENTAL STRESS AND ATHEROSCLEROSIS

In this study, cerebral blood flow and function were studied in the *Macaca fascicularis* during hypercapnia, hypoxia, and atherosclerosis (ref. 5). Techniques were used which have been previously described in the *Macaca mulatta* to measure cerebral blood flow with a Doppler ultrasonic flow transducer around the common carotid artery (refs. 8–13). The objective was to determine the early effects of atherosclerosis, produced by a 2 percent cholesterol diet, on the cerebral circulation and the cerebrovascular response to changes in perfusion pressure, hypercapnia, and hypoxia.

The results of this study indicated that autoregulation of cerebral blood flow was maintained during hypoxia and normocarbina in both control and cholesterol-fed monkeys. Both groups achieved similar levels of cerebral vasodilation during inhalation of 9 percent CO<sub>2</sub> in air. However, the time constant of cerebral vasodilation, the time required to achieve 67 percent of the response to CO<sub>2</sub> was significantly longer in the diet-fed monkeys. The mean time constant was  $61 \pm 15$  sec in the control group and  $157 \pm 29$  sec in the diet-fed group. Severe atherosclerotic lesions were observed in the aorta and in the coronary, femoral, brachial, and common carotid arteries in the diet-fed group. Gross lesions were not observed in the major cerebral arteries; however, mild-to-moderate subintimal accumulation of foam cells and vacuolation were observed in major cerebral arteries arising from the circle of Willis.

The results suggest that basic physiologic properties and responses of the cerebrovascular circulation may be modified in the *Macaca fascicularis* during the early stages of atherosclerosis. This may have a significant effect on cerebral function in aircrew members with early atherosclerosis if they are exposed to environmental stressors such as a sudden change in perfusion pressure to the brain during acceleration in a high performance aircraft.

## INSTRUMENTATION METHODS IN THE RHESUS MONKEY

A primate model using the *Macaca mulatta* was developed to evaluate cardiovascular performance and to define physiologic endpoints in a high-G air-combat maneuvering environment. Male rhesus monkeys were trained for 1 to 2 weeks to sit quietly in a primate restraint chair. Following adaptation to chair restraint, three surgical procedures were performed on each monkey, using aseptic technique and anesthesia. Anesthesia was induced with intravenous thiopental sodium and was maintained with a mixture of halothane, nitrous oxide, and oxygen.

Initially, an acrylic pedestal was surgically anchored to the skull of each monkey with four to six small stainless steel bolts. Techniques were modified from those described by Wolfe (ref. 14) for chronic head restraint and electrophysiologic recording in the awake rhesus monkey. Approximately 4 to 6 weeks after the pedestal was placed on the skull, a left thoracotomy was performed. A small solid-state pressure transducer was implanted on the endocardial surface of the left ventricle, ECG electrodes sutured on the heart, and a Doppler ultrasonic flow transducer placed around the ascending aorta. Transducer leads were passed subcutaneously to the back of the skull, anchored to the pedestal with dacron mesh and terminated in an electrical connector or in a plastic container which was attached to the pedestal with acrylic. Approximately 2 to 3 days prior to experimentation, catheters were introduced through the carotid artery and jugular vein

and positioned in the aortic arch and right atrium. The ends of the catheters were also secured to the pedestal and placed in the plastic container. These techniques minimize the complications of infection and secure the transducer leads and catheters from damage by the primates. From these transducers and catheters, the electrocardiogram, heart rate, arterial and central venous blood pressure, left ventricular pressure and  $dP/dt$ , and cardiac output were recorded in the conscious rhesus monkey.

## ACCELERATION STRESS

There are conflicting reports concerning the effects of high G and repetitive G maneuvers on myocardial pathophysiology in man in air-combat maneuvering. Electrocardiographic changes as well as extreme changes in blood pressure are observed in man during acceleration stress (refs. 3 and 4). A significant decrease in cardiac output has been reported during  $+G_z$  acceleration (refs. 15 and 16). Subendocardial hemorrhage has been observed in miniature swine (refs. 1 and 17), suggesting injury and changes in myocardial function which may result in reversible or irreversible pathophysiologic changes in the heart of man during acceleration stress. It is therefore necessary to conduct similar acceleration experiments in nonhuman primates in order to determine safe exposure limits and the etiology of myocardial pathophysiology in man during acceleration stress.

Ten male rhesus monkeys, 3 to 5 kg, were studied in the acceleration environment, using the techniques described above. Each rhesus monkey was placed in a specially designed primate chair in the gondola of the centrifuge. The monkey was in a sitting position, completely conscious, in order to subject him to the same G profiles which man is exposed to. The chair was mounted on a platform which tilted to simulate a tilt-back seat in the high-acceleration cockpit of a lightweight fighter. A blood pressure cuff was placed around the abdomen and inflated at the same schedule as a human anti-G suit. The primates were subjected to different G profiles, both gradual and rapid onset.

The first exposure to acceleration stress was a gradual onset, 1 G/15 sec, at a  $13^\circ$  back angle without the protection of an anti-G suit. This was performed in order to identify acceleration tolerance or blackout based on eye-level blood pressure (fig. 1). This particular primate had an unusually high G tolerance. Since it was his first exposure to acceleration stress, the run was terminated at 6 G. The preacceleration hypertension suggests that the monkey was excited and it probably accounts for the higher G tolerance. It indicates that training and adaptation to acceleration stress may often be necessary prior to exposing conscious primates and other animals to acceleration stress in experimental studies.

Each monkey was then exposed to repetitive maneuvering G forces, using actual F-4E or simulated F-15 air-combat maneuvers at seat back angles of  $13^\circ$ ,  $30^\circ$ ,  $45^\circ$ , and  $65^\circ$ . As the seat angle increases, the  $+G_x$  component of acceleration experienced by the subject increases and the  $+G_z$  component decreases. Each of these profiles was preceded and followed by an exposure to sustained G which was equivalent to the integral of the air-combat maneuver (fig. 2). Sustained G profiles have been used predominately in acceleration research in the past. Pilots, however, are exposed to varying repetitive maneuvering G forces with different onset rates in air-combat maneuvers. The profile shown in figure 2 permits comparison of the physiological responses to sustained and maneuvering G. Comparison of the physiological responses to the first sustained G profile with

the last in figure 2 also provides information regarding fatigue of the cardiovascular system at different seat angles.

Some of the physiologic responses to an F-4E ACM at a 65° seat angle are shown in figure 3. The ACM maneuver is approximately 100 sec long; 8 G is attained at two points in the maneuver. There are positive chronotropic and inotropic responses, illustrated by increases in heart rate and left ventricular dP/dt, respectively, which coincide or occur subsequent to the peaks in the G forces.

As the seat angle is increased, eye-level arterial pressure is maintained at a higher level (fig. 4). During the simulated F-15 ACM maneuver in figure 4, the onset rate is greater and peaks of 10 G are reached. There is little improvement at 30°, but, at 45° and 65°, protection is provided, which is particularly important in regard to eye-level pressure when peak G is attained. It should also be noted that arterial pressure is now within a normal range during the preacceleration period. This experiment was performed 11 days later using the same monkey described in figure 1.

Each experiment was concluded with a gradual onset to G at a 13° back angle to determine if repeated exposure to acceleration stress resulted in fatigue of the cardiovascular system (fig. 5). As the G time increased, resulting from multiple exposures to sustained and maneuvering acceleration, G tolerance, measured by eye-level pressure, decreased.

The results indicate that the rhesus monkey is a useful model to study the effects of gravito-inertial forces encountered by man during repetitive and maneuvering acceleration in new generation fighter-attack aircraft. The model permits investigation of damage mechanisms, risk limits, fatigue of the cardiovascular system, and pathophysiologic responses to acceleration. It has been demonstrated that increasing the seat back angle during maneuvering acceleration results in improved eye-level blood pressure. Repeated exposure to sustained and maneuvering acceleration indicates that fatigue occurs and cardiovascular compensation becomes inadequate. Subendocardial hemorrhage, however, has not been observed.

## CARDIOVASCULAR EFFECTS OF ENFLURANE AND HALOTHANE

All general anesthetic agents are known to depress the myocardium. This is true for halothane, the most widely used and accepted agent, and enflurane, the most recent to receive FDA approval. *In vitro* methods, using isolated cat papillary muscle, to compare the effects of enflurane and halothane on myocardial contractility, have provided conflicting results. While Brown and Crout (ref. 18) found enflurane to be more depressant than halothane, Shimosato *et al.* (ref. 19) found it to be less depressant. In our study, seven rhesus monkeys were chronically instrumented, using the techniques described earlier to compare the effects of enflurane and halothane, halogenated inhalation anesthetic agents, on cardiovascular function. The objective was to evaluate the relative depressant action of these agents in a more clinical setting. They were evaluated, first in the awake, conscious state, and then, after equilibration, at two different anesthetic levels. Gases were administered with oxygen. Ventilation was maintained to keep CO<sub>2</sub> within a normal range. End expired gas concentrations were analyzed by gas chromatography and were expressed in multiples of human minimum alveolar concentration (MAC) for comparison. Seventeen anesthetic exposures were recorded; 48 hr elapsed before a monkey received a second anesthetic. The order in which each monkey received each agent was alternated, as were anesthetic depths. Heart rate, cardiac output,

stroke volume, mean arterial pressure, central venous pressure, left ventricular pressure, maximum left ventricular dP/dt, and the latter divided by left ventricular developed pressure (dP/dt/P) were recorded or derived. These parameters were affected in a predictable, dose-related manner by both agents. Both halothane and enflurane significantly decreased heart rate, mean arterial pressure, left ventricular pressure, maximum dP/dt, and dP/dt/P. At equal MAC levels, no significant differences were detected; enflurane was as depressant to the heart as halothane.

## SUMMARY OF RESULTS

Nonhuman primates are useful models to study cardiovascular physiology in acceleration and biomedical research. Results of representative studies using two species, the *Macaca mulatta* (rhesus monkey) and the *Macaca fascicularis* (crab-eating monkey), have been described. The effects of atherosclerosis on cerebrovascular dynamics were investigated in the *Macaca fascicularis*. Cardiovascular instrumentation techniques were described in the *Macaca mulatta*. This species was used to study the effects of maneuvering acceleration stress and anesthetic agents on myocardial and cardiovascular function.

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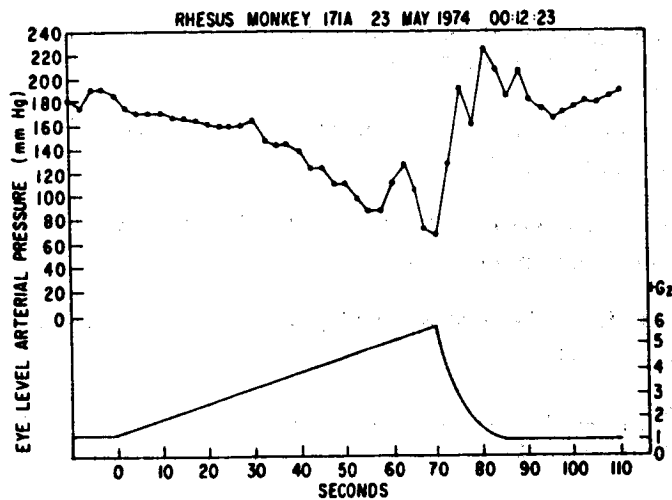


Figure 1.— Response in eye-level arterial blood pressure during gradual onset to G.

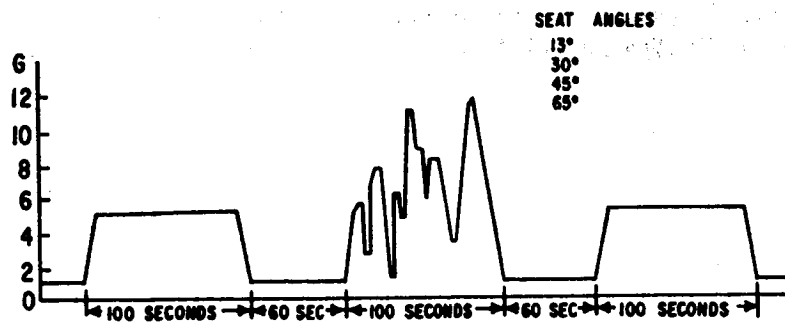


Figure 2.— F-15 computer-simulated air-combat maneuver and equivalent integrated sustained G experienced by each primate at each seat angle.

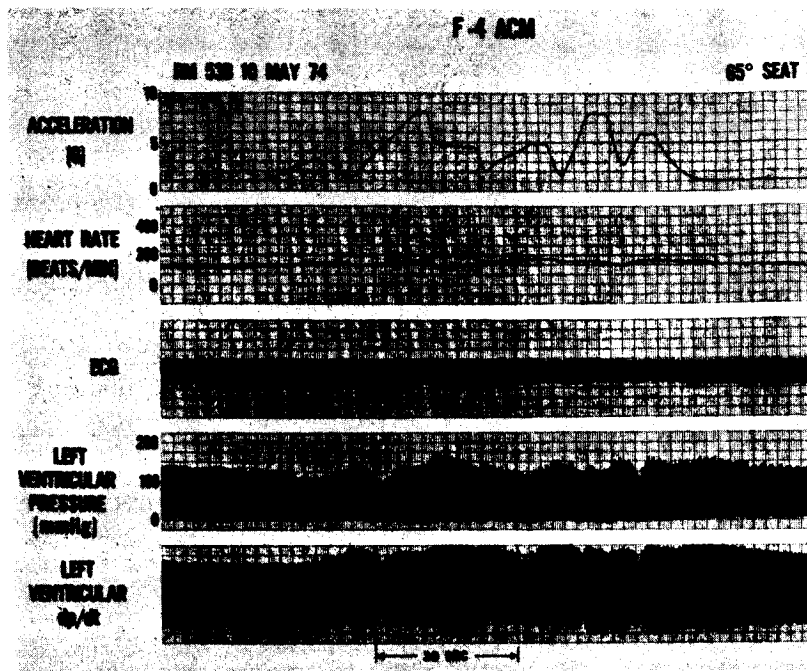


Figure 3.— Cardiovascular responses in a conscious rhesus monkey during exposure to an F-4E air-combat maneuver at 65° seat angle.

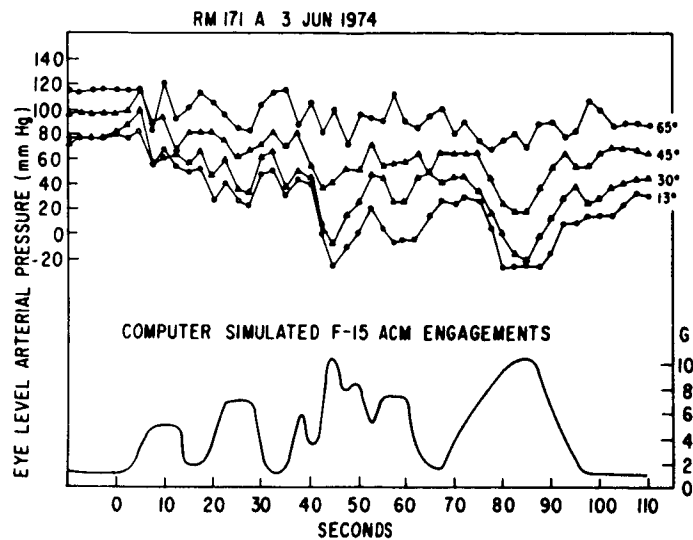


Figure 4.— Eye-level arterial pressure in a conscious rhesus monkey during exposure to an F-15 air-combat maneuver at different seat angles.

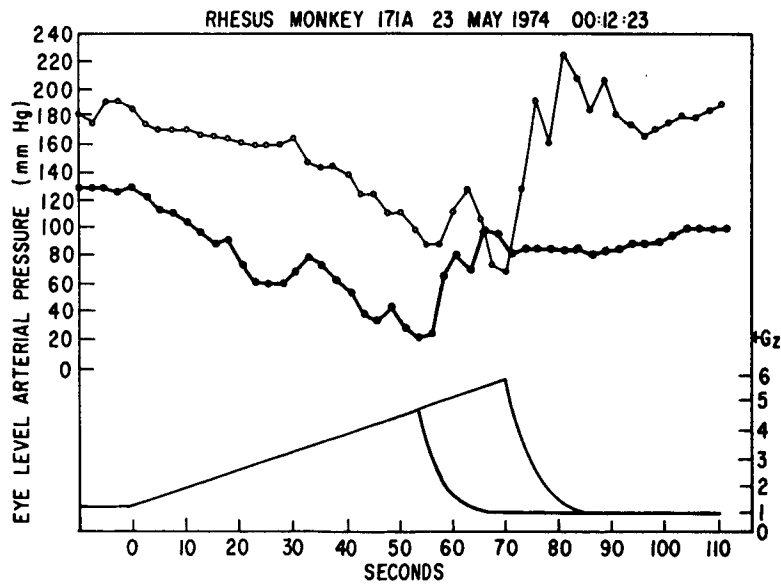


Figure 5.— Effects of repetitive exposure to sustained and maneuvering acceleration on eye-level arterial pressure. Light solid line (open circles) represents preexperimental run. Dark solid line (closed circles) represents post-experimental run.

## APPENDIX A

### CONFERENCE MINUTES

Richard Simmonds  
Ames Research Center

The Conference on the Use of Nonhuman Primates in Space was convened at the Ames Research Center at 8:30 a.m., December 2, 1974. Business was conducted as shown in the attached agenda (attachment 1). Persons attending the conference represented NASA Headquarters, NASA Field Centers, 2 other government agencies, and 11 nongovernment organizations (attachment 2 lists the attendees).

The stated goals of the conference were:

1. Summarization of the current status of NASA-sponsored nonhuman primate (NHP) research.
2. Definition of the need(s) for using NHP's in space-related biomedical experimentation.
3. Evaluation of various primate species as candidates for use in space research.
4. Definition of maintenance requirements for flying primates during the Shuttle era.
5. Discussion of the scientific objectives and requirements for Shuttle-era primate experiments.

In the opinion of this writer, goals 1 and 3 were completely accomplished while goals 2, 4, and 5 were only partially achieved. It was the consensus that one must know what specific experiment is to be accomplished, or at least what specific question is to be addressed, before one is able to define specific requirements and objectives. It was generally agreed that the objectives for life science research on the Shuttle must soon be defined in detail if critical planning for experiments is to be accomplished in time to provide specific guidelines for hardware design of programs in progress.

#### Monday, December 2

The entire day was devoted to formal presentations covering the historical background of space biology and the current status of NASA-funded NHP research. No attempt will be made in these minutes to summarize the individual formal presentations. As announced at the conference, it is our intent to publish the papers as a NASA publication and all attendees will be provided with a copy of the document when it is finished. In general, the papers were well done, informative, and well presented. (Some presentations were not received in time to be included in this compilation of papers.)

Following adjournment at 5:00 p.m., attendees were given the opportunity to visit the Pioneer 11 spacecraft control center.

#### Tuesday, December 3

The morning and part of the afternoon were again devoted to presentation of formal papers. Following the last paper, several general discussions were held, and these are summarized in the following paragraphs.

Dr. R. D. Johnson presented a review on future flight opportunities with emphasis on the Biomedical Experiment Scientific Satellite (BESS — a Shuttle-launched and -recovered, free-flying, long-duration satellite designed for exposing biological specimens to space-flight conditions for up to 6 months). Following Dr. Johnson's presentation, a lively debate ensued concerning the usefulness and requirements for a free-flying satellite such as BESS. Considerable controversy existed on the minimum number of animals which would ensure statistical validity of resulting data. All persons present agreed that one animal would be unacceptable, a majority agreed that two animals would be acceptable, and a vocal minority believed that five animals would be the minimum number necessary. It was pointed out that a young adult macaque monkey had been selected as the "design" species for the BESS, and discussion on this point resulted in the consensus that this selection was acceptable provided the specified weight be raised from 9–11 kg to 11–14 kg. Another point generating considerable discussion was the desirability of on-orbit hands-on access to the monkeys prior to reentry. It was the group opinion that the BESS program can be greatly improved if the vehicle can be designed to permit on-orbit hands-on access to the animals; however, it was also the consensus that the scientific value of long-duration exposure capability is so great that the BESS program should be pursued even without such in-flight access. It was pointed out by an attendee that BESS-type experiments should precede each significant increase in manned space-flight duration. Such procedures, once a workable satellite is designed, will permit more accurate predictions of the effects of ever-increasing space-flight duration on mammalian physiology.

Following the conclusion of the BESS discussions, Dr. Sandler presented a brief summary of the current status of biological studies in space. He noted that the last Soviet flight using a large mammal was in 1966 (two dogs) and the last U.S. flight was in 1969 (one monkey). He then pointed out that the reason for discontinuing the use of large mammals is apparently the lack of suitable flight-qualified animal maintenance hardware. Dr. Sandler concluded by noting that the cost of space biology will dictate that all experiments be of high scientific quality and merit.

Dr. Klein then noted that any animal experiment will be expensive, will probably be a significant percentage of the Life Sciences budget, and will be very visible within the agency and to the public. Therefore, regardless of the scientific intent, agency administrators and the public will look upon any such experiment as being related to manned space flight. For this reason we must be extremely careful in designing and planning experiments so that the chances of obtaining the designed data are maximized and the chances for misinterpretation of the results are minimized.

Dr. Jones concurred with Dr. Klein's comments and added that simplicity will be the key to low cost for future experiments. He then gave a brief summary of the pitfalls encountered by previous space biology projects, particularly the Orbiting Primate Experiment. He went on to explain that we must continually trade off the value of any anticipated returns from an experiment against the engineering complexity and cost. It was pointed out that some sort of "universal" modular animal housing system probably will be the least costly.

Following Dr. Jones' remarks, Dr. Simmonds asked the attendees to think about answers to the following questions and then adjourned the meeting for the day:

1. Is there any reason to use any nonhuman primate in space biomedical experiments?

2. If the answer to question 1 is yes, what specific research areas require the use of nonhuman primates and which primate species should be used?

3. Relative to flight modes, if we fly nonhuman primates, should they be restrained or unrestrained and how much implanted instrumentation is too much?

Wednesday, December 4

The discussions that ensued during this day were lively and broad ranging. Most conference participants entered into the debates with gusto, thus resulting in a frank exchange of ideas. In the interest of brevity and clarity, the day's discussions are summarized below in outline format.

*Need for nonhuman primates* – It was unanimously agreed that there is significant scientific justification for using NHP's in space biomedical studies. The usefulness of NHP's in general biomedical research is recognized by the American scientific community and the federal government by their establishment of, and continued support for, more than nine major primate research centers. The phylogenetically close relationship of NHP's to man, their relatively bipedal – at least upright – posture, and their anatomical, physiological, and biochemical similarities to man make them extremely useful surrogates for humans. In addition, the basic justifications for using any animal in biological research apply to the use of NHP's (e.g., use of invasive or hazardous techniques, critical control of experiment parameters, euthanasia of the subjects with subsequent histological and biochemical analyses of various parts of the animals, etc.). Discipline areas in which NHP's would be particularly useful include, but are not limited to: physiology (cardiovascular, vestibular, pulmonary, etc.), endocrinology, neurology, radiobiology, pharmacology, and pathology. Finally, from a biopolitical standpoint, the use of NHP's would be more "acceptable" to the general American public than other higher vertebrates such as the dog or cat.

*Nonhuman primate species of choice* – In trying to reach agreement on which NHP species would be acceptable candidates for use in space experiments, consideration was given to anticipated availability (including the animal's "endangered" status), size and weight of individuals and temperament, as well as, to the specifics of experimental requirements. After much deliberation it was concluded that the species which have been used in past space-related research programs are still the most logical candidate species. In descending phylogenetic order, these species are the chimpanzee (*Pan troglodytes*), baboon (*Papio* spp.), pigtail monkey (*Macaca nemistrina*), rhesus monkey (*Macaca mulatta*), cebus monkey (*Cebus* spp.), and squirrel monkey (*Saimiri sciureus*). It was noted that chimpanzees and baboons are large and very strong and would require large and hefty hardware which would probably be very costly. The squirrel monkey, although very suitable for space studies because of its small size (about 1 kg), is somewhat sensitive to environmental stress and would require very "fine-tuned" maintenance systems. It was again the consensus that an adult macaque monkey (about 11–14 kg) should be the model for the initial design of Shuttle animal maintenance hardware for NHP's. It is anticipated that a system sufficient to maintain an adult macaque could potentially be scaled up or down to accommodate other primate species.

Three other species of NHP's were mentioned which are worthy of further evaluation for their suitability as space subjects. They are the tarsier (*Tarsius* spp.), talapoin monkeys (*Cercopithecus* spp.), and gibbon (*Hylobates* spp.).

*Restraint versus nonrestraint* — It was the consensus that there is more than adequate justification for developing systems for flying both restrained and unrestrained NHP's. Experiments using one type of hardware can be designed to be complementary to studies utilizing the other hardware. Certain tests can only be accomplished in restrained animals (e.g., application of lower body negative pressure).

*Amount of implanted instrumentation* — There was no agreement as to how much implanted instrumentation is too much. Most participants concurred, however, that "end-to-end" flight simulations using complete experimental systems (hardware and fully instrumented animals) are mandatory in developing in-flight biological experiments. Such tests would indicate whether or not the animals were overinstrumented.

*Number of animals* — As noted above for BESS, it was unanimously agreed that one animal is insufficient for statistical analysis of resulting data, while most conferees agreed that a minimum of two animals would be adequate to permit valid conclusions. However, the consensus was that the optimal number of animals per treatment group is six. A minority of attendees was of the opinion that five animals would be the least number which would permit valid statistical analysis of flight data.

*In-flight manipulations* — It is anticipated that at least the following procedures should be accomplished in-flight on NHP's, particularly those flown on manned missions: determination of body mass, biopsies, blood collection, injection and/or infusion of various substances (e.g., drugs, isotopes, etc.), provocative cardiovascular and/or vestibular tests, autopsies and/or surgery (after experience is gained in flying NHP's), and preservation of dead animals.

*Miscellaneous* — Many conference participants expressed the opinion that regardless of the type of study, when NHP's are used, the investigator must take into account the species' social and psychological characteristics when designing the experiment. For that matter, consideration of the animals' "feelings" is of utmost importance in the success of any in-flight maintenance system. Such considerations might require that in-flight caging systems permit auditory, visual, and/or physical contact between NHP's flown in space.

It was also the consensus that unless an experimental protocol requires otherwise, all animal maintenance hardware should be designed to give NHP's the same space required by current federal animal welfare laws. The inherent stresses of space flight are bad enough, and we should not compound the experimental variables by overly confining the animals.

There was some discussion as to the physiological effect of the air flow conceptually proposed for the in-flight waste management systems for unrestrained animals. Some concern was expressed that such a system might be stressful to the animals and might interfere with zero-G studies. It was generally "felt" that the possible interference with gravitational studies is negligible but that there is insufficient data to predict the physiological stress of such systems.

The problem of contamination of the crew compartment atmosphere was addressed, and it was the consensus that a unidirectional air flow system (i.e., from crew compartment to the animal housing unit, through a biological filter, and into the crew compartment environmental control system) would be biomedically safe and physiologically satisfactory for the average NHP experiment.

## ATTACHMENT 1

### PROGRAM

*Monday, December 2, 1974*

- |            |   |
|------------|---|
| 8:15       | Assemble  |
| 8:30       | Welcoming Remarks<br><i>H. Sandler, W. Jones, J. Sharp</i>  |
| 8:40       | Definition of Meeting Objectives and Ground Rules<br><i>R. Simmonds</i>                             |
| 9:00       | History of Use of Nonhuman Primates in Space Flight<br><i>H. Sandler</i>                            |
| 9:30       | Physiological Studies in Space with Nonhuman Primates Using the Monkey Pod<br><i>N. Pace</i>        |
| 10:15      | The Orbiting Primate Experiment<br><i>G. Bourne, M. N. Golarz de Bourne, and H. McClure</i>         |
| 11:00      | Discussion  |
| 12:00 Noon | Lunch   |
| 13:30      | The Rhesus Monkey as a Flight Candidate<br><i>G. Bourne, M. N. Golarz de Bourne, and H. McClure</i> |
| 14:00      | Cardiovascular Studies Using the Rhesus Monkey<br><i>H. L. Stone and H. Sandler</i>                 |
| 14:30      | The Chimpanzee as a Flight Candidate<br><i>M. Keeling</i>   |
| 15:00      | The Effects of Transverse Acceleration on Chimpanzees<br><i>E. Wood</i>                             |
| 15:30      | Biorhythms and Space Experiments with Nonhuman Primates<br><i>C. Winget</i>                         |



- 16:00      **Vestibular Function and Sleep in Space Experiments with Monkeys**  
*A. Perachio*
- 16:30      **Discussion**
- 17:30      **Visit to Pioneer Mission Control Center**
- 18:30      **Return to motel**

*Tuesday, December 3, 1974*

- 8:15      **Assemble**
- 8:30      **Veterinary Aspects of Using Nonhuman Primates in Space**  
*R. Simmonds*
- 8:45      **The Squirrel Monkey as a Flight Candidate**  
*K. Brizzeé*
- 9:15      **The Capuchin Monkey as a Flight Candidate**  
*C. Winget*
- 9:45      **The Pigtail Monkey as a Flight Candidate**  
*N. Pace*
- 10:15      **Cardiovascular Studies Using the Anubis Baboon**  
*S. Vatner*
- 10:45      **The Baboon as a Flight Candidate**  
*S. Vatner*
- 11:15      **(A) Cardiovascular Studies Using the Chimpanzee**  
*E. Hawthorne*  
**(B) The Chimpanzee as a Flight Candidate**  
*E. Hawthorne and J. Hinds*
- 11:45      **Other Nonhuman Primate Candidates**  
*G. Bourne and M. N. Golarz de Bourne*
- 12:00 Noon      **Lunch**
- 13:30      **Instrumentation**  
*E. P. McCutcheon*
- 14:00      **Discussion**
- 14:30      **Future Space Vehicles Available**  
*R. D. Johnson*

**15:30**      **Discussion by whole group**

- 1. Advantages of using primates instead of other animals. Summary of Russian experiments with dogs – *R. Simmonds***
- 2. If primates are to be used, nature of experiments and what they might be expected to show. Could or should other surrogates for humans be used and for what parameters?**
- 3. Discussion of unified approach for NASA-sponsored primate research.**

**17:00**      **Return to motel**

**19:00**      **Cocktails and Dinner**

***Wednesday, December 4, 1974***

**8:30–15:30 Continuation of Discussion and Production of Recommendations**

## ATTACHMENT 2

### ATTENDEES

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